Science Moving Forward

A progress report to the FDA Science Board

U.S. Department of Health and Human Services
U.S. Food and Drug Administration

FDA Science Moving Forward

— Progress Report to the FDA Science Board's Science Looking Forward Subcommittee

FDA Mission Statement

FDA is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.

FDA is also responsible for advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medicines and foods to maintain and improve their health. FDA also has responsibility for regulating the manufacturing, marketing, and distribution of tobacco products to protect the public health and to reduce tobacco use by minors.

Finally, FDA plays a significant role in the nation's counterterrorism capability. FDA fulfills this responsibility by ensuring the security of the food supply and by fostering development of medical products to respond to deliberate and naturally emerging public health threats.

Executive Summary

As the Science Board's 2007 report *FDA Science and Mission at Risk* anticipated, rapid developments in scientific areas such as genomics, systems-based biology, precision medicine (also known as personalized medicine), informatics, and tissue- and stem cell-based therapy have dramatically increased the complexity of the scientific challenges facing FDA. Furthermore, recent legislation has set new standards, granted new authorities, and established ambitious goals for the Agency. For example, the FDA Amendments Act of 2007 called for the establishment of the Office of the Chief Scientist to provide FDA with strategic vision and leadership for our regulatory science programs and support in identifying our scientific priorities.

The establishment of the Office was only one of many far-reaching organizational changes FDA has made since the Science Board's report. For example, FDA established:

- the Office of Counterterrorism and Emerging Threats to facilitate medical countermeasures development and advance regulatory science within this area.
- the Office of Scientific Professional Development to provide leadership and support for recruiting and fostering top talent and providing innovative skills development programs to prepare FDA staff to address new regulatory challenges.
- the Office of Regulatory Science and Innovation to lead and support the Agency in fostering the creation and use of innovative technologies in product development and evaluation.
- the Office of Foods and Veterinary Medicine to lead a functionally unified Foods Program and enhance FDA's ability to meet today's great challenges and opportunities in food and feed safety as well as nutrition.

FDA has implemented many of the Science Board's recommendations for improving the scientific infrastructure, management, and application of regulatory science to enhance our regulatory mission. At the same time, FDA has expanded its use of existing mechanisms to develop new collaborative programs.

This report details how FDA has accelerated efforts to develop new approaches to engaging in synergistic collaborations both intramurally and with other government agencies, academia, industry, patient organizations, professional societies, and other stakeholders. We discuss our efforts to attract, develop, and retain top scientific talent to the Agency and to enhance scientific training and continuing education opportunities for FDA staff. In the final section of our report, we highlight examples of FDA scientific accomplishments, organized according to the eight priority areas that FDA identified in its Strategic Plan. We hope that this report is helpful to the Science Board in its review of FDA's efforts to advance regulatory science.

Introduction

Background

From its origins as a small office in the Department of Agriculture's Bureau of Chemistry a little more than a century ago, the Food and Drug Administration (FDA) has grown to an agency that is responsible for overseeing more than $2 trillion in medical products, food, and other consumer products.[1] Globalization, emerging technologies, and rapid advances in the sciences that underlie FDA-regulated products have transformed FDA's regulatory landscape and expanded the scope of our mission. In this changing environment, as FDA monitors the nation's food supply, drugs, biologics, devices and tobacco products it is critical that we stay abreast of these advances in science and technology. Active engagement with our public- and private-sector partners will help us leverage our scientific resources to ensure that safe, innovative treatments and cures get to the people who need them when they need them.

Since its establishment in 1992, FDA's Science Board has provided us with input on these emerging scientific and technical developments and how best to prepare for their impact. The Science Board's 2007 report *FDA Science and Mission at Risk* appropriately emphasized that rapid developments in scientific areas such as genomics, systems-based biology, precision medicine, informatics, and tissue- and stem cell-based therapy would increase the complexity of FDA's work. Since that report, many of these technologies have entered FDA's regulatory portfolio, a few examples of which are cited below:

- FDA is receiving an increasing number of stem cell-based products for evaluation.
- An FDA advisory committee has considered medical interventions involving manipulation of the mitochondrial genome that would prevent the transmission of severe mitochondrial diseases.
- FDA is seeing a growing number of submissions for medical devices that use computer simulations to describe how the device performs.
- FDA is increasingly using next-generation sequencing to identify sources of microbial contamination in food and other regulated products.
- FDA is receiving a growing number of regulatory submissions in which genomics data are considered in the approval and labeling supporting the development of genomically targeted therapeutics to further personalize medicine.

In the last five years, FDA has strengthened and repositioned our regulatory science programs, incorporating many of the Science Board's 2007 recommendations to ensure our readiness to meet these new and emerging scientific challenges. We now seek the Science Board's feedback, through the FDA Science Looking Forward subcommittee, on the following three areas:

[1] Hamburg MA and Sharfstein JM, (2009). The FDA as a Public Health Agency. *N Engl J Med* 360(24):2493-5.

- Whether the fundamental changes that FDA has made to our regulatory science programs, including implementation of our Strategic Plan for Advancing Regulatory Science, have been a success and whether FDA should consider any other programmatic changes.

- What opportunities, strategies, and frameworks for collaboration, will best advance FDA's mission;

and

- Whether FDA has taken sufficient steps to strengthen our scientific workforce and whether additional steps may be necessary.

FDA's Unique and Critical Role in Advancing Regulatory Science

Regulatory Science is the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products.[2]

The term *regulatory science* is relatively new, but FDA's practice and application of regulatory science is as old as FDA itself. Although the Hygienic Table (*poison squad*) of volunteer tasters established in 1902 by Harvey Wiley was a rather crude way to test the safety of food preservatives, science matured and flourished in the nascent agency.

By the early 21st century, novel product development, based on accelerating breakthroughs in science and technology, was outpacing the science needed to effectively evaluate the resulting products. In 2004, FDA released its landmark report *Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products*.[3] The report called for collective action from all stakeholders to develop the new tools and methods necessary to evaluate and predict the safety, effectiveness, and manufacturability of new medical products.

The 2007 FDA Science Board report, *Science and Mission at Risk,* took a comprehensive look at the scientific foundation and infrastructure required for FDA to effectively evaluate *all* of its products in a world where science and technology are evolving at an increasingly rapid rate.

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[2] Tobacco products are fundamentally different from all other FDA-regulated products. Some language that applies to the products that FDA regulates (e.g., access, safety, and quality) does not apply to tobacco products in the same way. Expanded research is leading the way for science-based regulation of the manufacture, marketing, and distribution of tobacco products, which can help FDA reduce sickness and death from tobacco use.

[3] FDA (2004). *Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products*. Available at: http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/ucm113411.pdf. Accessed on May 23, 2014.

The report's broad recommendations called for:

- Realigning the science organization to better manage new science
- Strengthening the science base
- Increasing the use of appropriate modeling and
- Enhancing the scientific workforce.

FDA has implemented many of the Science Board's recommendations for improving the infrastructure, management, and application of regulatory science to enhance its regulatory mission.

Taking note of the Science Board's recommendations, FDA launched the Advancing Regulatory Science Initiative (ARS) in 2010, building on the achievements of existing Agency programs, like the Critical Path Initiative's groundbreaking efforts to transform the way medical products are developed, evaluated, and manufactured. Recognizing the success of the Critical Path model, ARS expanded its scope to encompass all FDA-regulated activities and every dimension of regulatory science, including postmarket surveillance.

While basic science is concerned with discovering fundamental mechanisms, regulatory science's is focused on developing and applying the best available scientific data, knowledge, methods, and tools to reduce uncertainty and make regulatory evaluation and decision-making more efficient and consistent. Regulatory science supports science-based decision-making to ensure public access to products that are manufactured or processed under conditions of consistent high quality and monitored to ensure their safety and quality during real-world use. And given FDA's diverse responsibilities and the rapid evolution of emerging sciences and technologies, the scope of regulatory science as practiced by the Agency is broad and diverse. Examples include:

- A new portable tool adapted by FDA's regulatory scientists to rapidly test raw materials and finished products in the field
- A new standard for determining the bioequivalence of locally acting drugs
- New analytical methods that enable FDA to monitor newly identified product contaminants or identify the source of disease-causing pathogens in FDA-regulated products or foods

In pursuit of our goals, regulatory science at FDA includes intramural research and extramural collaborations, with other government agencies,[4] academia, non-profit organizations, patient advocacy groups, and industry, where possible, to leverage intellectual capital and physical resources.

[4] For example, the National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC), and the U.S. Department of Agriculture (USDA).

To fulfill our myriad regulatory responsibilities, FDA must:

1. Be proactive in addressing emerging technologies that may become the regulated products of the future
2. Remain current on new science and technology, so FDA can use the best available tools to evaluate existing and new products
3. Make innovative contributions to new science and technology that reflect our knowledge of the regulatory needs and limiting factors in product development
4. Remain positioned to respond rapidly to public health emergencies involving our regulated products

New mandates from Congress, together with the rapid pace of scientific and technological advances, make it imperative that FDA aggressively incorporate the most current regulatory science into our oversight activities. This, combined with FDA's unique blend of regulatory perspective, broad access to often proprietary data, and a strong scientific knowledge base and infrastructure, will ensure that FDA remains the world's preeminent consumer product regulatory agency.

Section A. Build a Strong Foundation for Regulatory Science

Federal legislation defines the broad requirements, goals, authorities, and boundaries that govern FDA actions. FDA, in turn, develops a regulatory framework to achieve the intent of the law. This requires the development and application of new knowledge, tools, standards, and procedures. Recent legislation that has set new standards, granted new authorities, and established ambitious goals for new regulatory pathways includes the following:

- The FDA Amendments Act of 2007 (FDAAA)
- The Family Smoking Prevention and Tobacco Control Act of 2009
- Title VII of the Patient Protection Affordability and Accountability Act of 2010
- The Food Safety Modernization Act of 2011 (FSMA)
- The FDA Safety and Innovation Act of 2012 (FDASIA)
- The Drug Quality and Security Act of 2013 and
- The Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA)

The successful implementation of each of these laws requires FDA to break new scientific ground through application of the latest scientific developments and emerging technologies to build a scientifically sound framework for implementing new requirements. For example:

- FDA was charged with developing a new regulatory framework for review of *biosimilar* and *interchangeable* biologic products that required the Agency to develop the scientific standards for determining these endpoints.
- Although the concept of bioequivalence is defined in regulation, FDA was charged with developing the science and providing guidance on specific bioequivalent methods for drugs that act locally.
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- Tobacco regulations require FDA to use a population/public health standard that takes into account both users and non-users.
- FSMA gave FDA a mandate to implement a system that emphasizes prevention and prioritizes food safety challenges based on the risk they present to public health.
- PAHPRA included important provisions to clarify FDA's authority to allow for certain preparedness activities and rapid deployment of certain FDA-approved medical countermeasures (MCMs). These include extending the shelf-life of MCMs stockpiled for use in a public health emergency, waiving cGMP requirements, or issuing an order to allow emergency dispensing without an individual prescription.

Beyond implementing new legal mandates in a scientifically sound way, FDA faces additional challenges from products involving new areas of science and technologies that are complex to regulate and hard to incorporate into the regulatory review process. The newer and more innovative a technology is, the less

validated it is. And validation is important to verify equivalence and comparability to replace compendial methods.[5]

New science and technology are increasingly the subject of regulatory submissions. Examples include 3-D printing,[6] devices incorporating nanotechnology and wireless controls, targeted drug therapies, next-generation sequencing technology, stem cell-derived and gene therapy products, genetically modified organisms, and an increasing diversity of novel tobacco products. In addition, these new technologies are giving FDA powerful new tools and approaches to address long-standing regulatory science challenges more effectively:

- Genomic tools are being used to identify more rapidly the source(s) of food-borne illness, to identify microbial contaminants in biologics, drugs, and devices, and to monitor and understand the development of antimicrobial resistance.
- Complex modeling tools are harnessing diverse sources of data to develop risk models to focus inspectional resources more effectively.
- New hand-held technologies are enabling field inspectors to identify key contaminants in commodities *before* they become components of FDA-regulated products.
- Advanced analytical technologies help FDA identify and understand the key structural attributes of complex protein therapeutics and make it possible to rapidly identify chemical contaminants and adulterants.

Advanced analytical instrumentation and methodology have been critical for quickly identifying adulterants in products ranging from heparin and animal feed to infant formula. (Table 1 provides examples of FDA emergency responses.)

This rapidly evolving regulatory and scientific landscape underscores the heightened importance of regulatory science. To meet this growing challenge, FDA has put in place the essential building blocks needed to support a stronger, proactive, and responsive regulatory science program. In the sections below, we have defined our goals and taken the following concrete steps towards reaching them:

1. Provide Strategic Leadership and Vision for Regulatory Science
2. Establish Regulatory Science Priorities
3. Optimize Organization, Governance, and Review
4. Enhance Resources and Infrastructure
5. Develop New Mechanisms and Programs to Leverage External Expertise

[5] e.g., 21 CFR 610.9

[6] FDA (2013). *Paving the Way for Personalized Medicine*, p. 9. Available at: http://www.fda.gov/downloads/scienceresearch/specialtopics/personalizedmedicine/ucm372421.pdf. Accessed on April 18, 2014.

1. Provide Strategic Leadership and Vision for Regulatory Science

The FDA Amendments Act of 2007[7] called for establishing the Office of the Chief Scientist (OCS) and appointing an FDA Chief Scientist charged with working internally and externally to provide strategic leadership and advocacy for regulatory science and FDA scientists. The Chief Scientist is the primary point of contact for FDA's cross-cutting scientific priorities. He or she forges important and mutually beneficial partnerships with sister Federal agencies; creates new mechanisms and programs for engaging and funding external efforts to advance regulatory science; enhances professional development, training opportunities, and peer review for FDA scientists, visiting fellows, and external stakeholders; coordinates FDA's preparedness for, and response to, rapidly emerging public health crises involving FDA-regulated products; and leads the FDA dialog on cross cutting issues.

In October of 2010, FDA released the white paper *Advancing Regulatory Science for Public Health*, which outlined a broad vision for advancing regulatory science and unleashing its potential to improve public health. It assigned a key role in this process to the Chief Scientist to "coordinate internal and external outreach to identify critical regulatory science and innovation needs and develop a strategic plan for science at FDA"[8] and asked the FDA Science Board to "review and inform the scientific strategic plan and regulatory science priorities."

2. Establish Regulatory Science Priorities

FDA will advance regulatory science to speed innovation, improve regulatory decision-making, and get products to people in need. 21st-century regulatory science will be a driving force as FDA works with diverse partners to protect and promote the health of our nation and the global community.[9]

Advancing regulatory science must start with identifying key scientific hurdles and knowledge gaps, followed by a clear articulation of the priorities.

[7] FDA Amendments Act of 2007, Sec. 602. Available at: http://www.gpo.gov/fdsys/pkg/PLAW-110publ85/html/PLAW-110publ85.htm. Accessed on April 18, 2014.
[8] U.S. Food and Drug Administration (2010). *Advancing Regulatory Science for Public Health*. Available at: http://www.fda.gov/downloads/scienceresearch/specialtopics/regulatoryscience/UCM228444.pdf. Accessed on April 18, 2014.
[9] Vision statement in FDA's August 2011 Strategic Plan for *Advancing Regulatory Science at FDA, pg. 6.* Available at: http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RegulatoryScience/UCM268225.pdf. Accessed on May 23, 2014.

Table 1. Recent Examples of Public Health Crises and FDA Response

In addition to the proactive regulatory science efforts outlined in this plan, a strong infrastructure is essential to ensure FDA's readiness to respond rapidly and effectively to public health emergencies. Headlines are replete with accounts of the major scientific role FDA plays in addressing such crises:

2007

Counterfeit glucose test strips: initiated Class I recalls and performed hazard evaluations pertaining to manufacturing, storage conditions, and clinical use of glucose strips

Melamine-contaminated pet food: FDA's Office of Criminal Investigations led to indictment by federal grand jury of foreign and U.S. businesses involved in adulteration

2008

Contaminated heparin: worked with WEAC, academia, and industry to rapidly characterize and identify the contaminant (oversulfated chondroitin sulfate) and rapidly developed and deployed necessary testing methods

Outbreak of Salmonella: coordinated with CDC, Mexican authorities, state regulatory agencies, and food industry groups to protect public from threat of affected food products

2009

Exposure to bisphenol-A through use of food packaging and medical devices: investigated potential for leaching of BPA in food packaging and medical devices including pediatric devices

Outbreak of human Influenza A 2009 H1N1 virus: performed initial human serology to identify strains; developed candidate vaccine seed strains; developed and distributed reference reagents used for potency testing of H1N1 vaccine; and developed a guidance document to help IVD manufacturers submit EUAs for diagnostic tests to detect this viral pathogen

2010

Deepwater Horizon oil spill: developed methods to monitor seafood contamination and evaluated the impact of oil-contaminated residues in edible tissues of seafood on the human intestinal microbiota

Outbreak of *Salmonella* Enteritidis: partnered with CDC to identify and respond to a *Salmonella* enteritidis outbreak in eggs that affected multiple states

2011

Earthquake and Tsunami, Honshu, Japan: conducted radiation testing of foods and commodities

Necrotizing Enterocolitis (NEC) in premature infants: Identified 22 infants who developed NEC following consumption of a thickening agent in infant formula and breast milk and conducted extensive product surveillance and public messaging on use of these products

Hurricane Irene: responding to flooding and damage to regulated food products in northeastern states, provided guidance on disposition of products affected by flood waters

2012

***Salmonella* Bareilly multistate outbreak associated with scrape tuna:** investigated outbreak of salmonella that resulted in hundreds of salmonella infections due to contaminated yellow fin tuna. Multistate and international investigations resulted in product recall and public messaging.

Compounding pharmacy fungal meningitis outbreak: worked closely with CDC, several state health departments, and the Massachusetts Board of Pharmacy to investigate the scope and cause of the outbreak.

Hurricane Sandy: conducted field inspections and public messaging on safety due to impact on regulated products

2013

Avian Influenza A (H7N9) and Middle East Respiratory Syndrome Coronovirus (MERS-CoV): issued emergency use authorizations for diagnostic tests to facilitate preparedness efforts for H7N9 and MERS-CoV, and studied genetic predictors of transmissibility in H7N9

2014

Ebola response: helped expedite the development and availability of medical products with the potential to help bring the Ebola epidemic in West Africa under control

The *Advancing Regulatory Science for Public Health* report identified broad priority focus areas for FDA. Subsequently, FDA's product centers and offices identified their respective core scientific priorities, which have been outlined in public documents that articulate science priorities and strategic plans.[10]

Bringing these efforts together at the Agency level enabled OCS and the Senior Science Council (see section on Governance and Review) to develop the Strategic Plan for Advancing Regulatory Science at FDA in 2011. This plan contained eight scientific priorities that provide guidance for proposals and inform the review of competitive grant applications from FDA scientists and those outside the Agency; a ninth area was added in 2013.

More recently, in compliance with regulatory science provisions in FDASIA and FSMA, FDA developed cross-cutting strategic plans for the medical product centers and the Office of Foods and Veterinary Medicine (OFVM). In response to requirements in FDASIA, the 2013 Strategy and Implementation Plan for Advancing Regulatory Science for Medical Products includes metrics against which FDA will report progress in advancing regulatory science for medical products for fiscal years 2014 and 2016. The Foods and Veterinary Medicine Strategic Plan 2012-2016 outlines seven strategic program goals, each encompassing its own key objectives, as well as nearly 100 specific initiatives aimed at achieving goals and objectives.

FDA's 8 Scientific Priority Areas*

1. Modernize Toxicology to Enhance Product Safety
2. Stimulate Innovation in Clinical Evaluations and Precision Medicine to Improve Product Development and Patient Outcomes
3. Support New Approaches to Improve Product Manufacturing and Quality
4. Ensure FDA Readiness to Evaluate Innovative Emerging Technologies
5. Harness Diverse Data through Information Sciences to Improve Health Outcomes
6. Implement a New Prevention-Focused Food Safety System to Protect Public Health
7. Facilitate Development of Medical Countermeasures to Protect Against Threats to U.S. and Global Health and Security
8. Strengthen Social and Behavioral Science to Help Consumers and Professionals Make Informed Decisions about Regulated Products

*In 2013, FDA added a ninth, *Strengthening the Global Product Safety Net*

[10] FDA (2011). *CDER Science and Research Needs Report 2011*. Available at: http://www.fda.gov/downloads/drugs/scienceresearch/ucm264594.pdf. Accessed on April 18, 2014; *Center for Biologics Evaluation and Research Strategic Plan For Regulatory Science And Research, 2012-2016*. Available at: http://www.fda.gov/downloads/biologicsbloodvaccines/scienceresearch/ucm303542.pdf. Accessed on April 18, 2014; *2014 - 2015 Strategic Priorities, Center for Devices and Radiological Health*. Available at: http://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cdrh/cdrhvisionandmission/ucm384576.pdf. Accessed on April 18, 2014; *Center for Food Safety and Applied Nutrition Science and Research Strategic Plan*. Available at: http://www.fda.gov/Food/FoodScienceResearch/ResearchStrategicPlan/default.htm. Accessed on April 18, 2014; *Tobacco Regulatory Science: Research to Inform Regulatory Action at the Food and Drug Administration's Center for Tobacco Products*. Available at: http://ntr.oxfordjournals.org/content/early/2014/03/16/ntr.ntu038.abstract. Accessed on April 18, 2014.

3. Optimize Organization, Governance, and Review

FDA realigned and revitalized scientific governance bodies and peer review procedures and created new working groups to more effectively address areas of rapidly emerging technological and scientific development. Some critical organizational changes since the FDA Science and Mission at Risk Report were the following:

Changes Within OCS

FDA created the **Office of Regulatory Science and Innovation** (ORSI) within OCS to provide strategic leadership, coordination, infrastructure, and support for excellence and innovation in regulatory science. ORSI has developed a number of critical internal and external programs and processes to identify knowledge gaps in regulatory science and address them through support of high-quality, peer-reviewed scientific research, programs, and related activities, within and outside FDA.

ORSI also provides an organizational home, leadership, and support for a number of FDA-wide scientific committees and working groups. Through the activities of these cross-cutting bodies, ORSI:

1. Fosters the creation and use of innovative technologies in product development and evaluation
2. Explores the need for core scientific capacity and infrastructure
3. Seeks input from FDA programs, stakeholders and outside advisers, including the FDA Science Board

ORSI also houses FDA's **Office of Technology Transfer**, which will be responsible for the full spectrum of technology transfer activities for the Agency effective FY 2016.

FDA established the **Office of Counterterrorism and Emerging Threats** (OCET)[11] to facilitate MCM development and advance regulatory science within this area. The Office meets a growing need to facilitate the development and availability of safe and effective public health emergency MCMs and to establish policies to safeguard medical products from adulteration and prevent disruption of supplies as a result of terrorist activities.

In addition to leading FDA's emergency use authorization (EUA) activities related to public health emergencies, in 2010 OCET launched FDA's Medical Countermeasures initiative (MCMi). Building on programs already underway in FDA medical product centers, MCMi coordinates FDA's efforts to promote the development of and access to MCMs by establishing effective regulatory policies and mechanisms to facilitate their timely access and availability.

A critical part of this effort involves advancing regulatory science to pursue solutions to complex scientific regulatory challenges. This enables FDA to harness cutting-edge science and apply innovative approaches to the regulatory process to help improve MCM development timelines and success rates.

[11] The function of OCET pre-dates September 11, 2001, when it was called the Office of Counterterrorism Policy and Planning.

Since its inception, the **Office of Scientific Professional Development** (OSPD) has provided leadership and support for FDA efforts to recruit and foster top talent by providing innovative skills development programs to prepare FDA staff to successfully address the regulatory challenges presented by new areas of science and medicine.

OSPD has supported the building blocks that will underpin greatly expanded outreach efforts to actively engage our external collaborators and stakeholders in training and educational programs constructed around regulatory science. As Section C details, programs such as the Commissioner's Fellowship Program and university-based educational programs in regulatory science within the Centers of Excellence in Regulatory Science and Innovation enhance both the pool of talent for FDA positions and the understanding of regulatory science among those who become our stakeholders.

Formed in 2009, the **Office of Scientific Integrity** (OSI) reports to the Chief Scientist and works with the Office of the Commissioner and FDA's product centers to ensure that the Agency's policies and procedures concerning scientific integrity at FDA are current and applied across the Agency. Together with our product centers and offices, OSI reviews and works to resolve both informal and formal scientific disputes. OSI evaluates scientific differences that are not resolved at the center level and advises the Chief Scientist and other senior FDA leadership on appropriate responses. OSI also provides oversight and policy development related to research involving human subjects conducted by or supported by FDA and manages the Research Involving Human Subjects Committee, FDA's IRB.

The **National Center for Toxicological Research** (NCTR) was placed within OCS in recognition of its significant role in addressing cross-Agency regulatory science priorities. The FDA-wide laboratory research center, located in the Little Rock, Arkansas area, is equipped with state-of-the-art instrumentation and support facilities to conduct scientific research studies. Expertise is wide-ranging, including specialized toxicological evaluation design, using chemistry, pharmacology, microbiology, neurobiology, systems biology, in silico modeling, data mining, and biomarker development. The major areas of focus are designing studies to fill data gaps required for regulatory decisions and evaluating and adapting newly emerging tools of toxicology for use in the regulatory environment. NCTR also trains colleagues and the next generation of scientists from the national and international arena on the regulatory research paradigms that support regulatory decisions.

To more effectively align the recognized scientific mandates of the **Office of Women's Health** (OWH) and the statutorily[12] created **Office of Minority Health** (OMH) with the larger FDA scientific community, these offices were incorporated into OCS. Both OWH and OMH have clearly articulated cross-cutting regulatory science programs that benefit from ongoing interactions with scientists from across FDA and with external partners. OWH and OMH both have made significant investments in regulatory science needed to better understand and improve the health of women and minorities.

[12] As mandated by the Affordable Care Act

Other Key Organizational Changes

In addition to the reorganization within OCS, the Commissioner also reorganized FDA's structure into Directorates that report to the Commissioner. Establishment of the Directorates has enabled FDA to better align our regulatory science programs with our mission.

FDA created the **Office of Foods and Veterinary Medicine** (OFVM) in August of 2009 to lead a functionally unified Foods Program and enhance the Agency's ability to meet today's great challenges and opportunities in food and feed safety, nutrition, veterinary drugs, judicious use of antibiotics, antimicrobial resistance, and other critical areas. OFVM is an ideal platform from which to launch key initiatives to improve the effectiveness and efficiency of the regulatory science programs across the Centers for Food Safety and Applied Nutrition (CFSAN) and Center for Veterinary Medicine (CVM). The result has been a single, integrated regulatory science strategy that unifies the approach to prioritizing regulatory science needs, tracking and reporting progress, evaluating effectiveness, and coordinating food safety regulatory science programs with the Office of Regulatory Affairs (ORA) and NCTR.

In combining ORA with the Office of International Programs (OIP), the **Office of Global Regulatory Operations and Policy** (OGROP) provides strategic leadership and policy direction to FDA's domestic and international efforts to ensure the quality of products and oversee the safety and integrity of clinical trials. OGROP components are actively engaged with FDA's product centers in furthering the regulatory science critical to supporting global field operations, applying new technologies to developing and deploying methods to ensure the quality and authenticity of regulated products. A strong foundation of regulatory science leads to swift, decisive enforcement actions that withstand legal challenges.

The Office of Medical Products and Tobacco (OMPT) provides high-level coordination and leadership across the centers for drug, biologics, medical devices, and tobacco products. In addition, OMPT oversees several other Offices: Office of Special Medical Programs, Office of Combination Products, Office of Good Clinical Practice, Office of Pediatric Therapeutics, and Office of Orphan Products Development.

Governance and Review

Complementing the organizational changes described above are parallel improvements in the overarching governance of regulatory science, including committees, functions, and processes to provide focus to how we practice proposing, evaluating, and funding projects for relevance and quality, and how we review individual programs within FDA.

1. **The Senior Science Council (SSC).** Operational since the 1990s, the SSC was reorganized with new membership in 2009 as a dynamic working committee. The OCS-led SSC is composed of senior scientific leadership from OCS, all FDA centers, OFVM, ORA, OWH, OMH, the Office of Combination Products, the Office of Orphan Product Development, and OGROP. SSC members also serve on FDA scientific working groups that form to address emerging technologies, including genomics and nanotechnology.

Charged with addressing and identifying solutions to cross-cutting regulatory science issues, the SSC revised its mission to include the following:

- Developing overarching regulatory science priorities (the SSC drafted and coordinated FDA's Regulatory Science Strategic Plan)
- Providing scientific peer review of research proposals for certain FDA-wide intramural grant programs, such as the Chief Scientist Challenge Grant Program
- Developing policy recommendations as needed to support FDA's regulatory science program
- Developing key external reports, such as the FDASIA Regulatory Science Strategic Plan
- Providing roadmaps for implementing new requirements related to the conduct of regulatory science
- Providing a forum for cross-cutting discussions of emerging science and technology

Members serve as a key communication link between their center's or office's senior leadership, scientific committees, and scientific staff. The SSC identifies opportunities for closer cooperation and coordination in cross-cutting areas of regulatory science. For example, last year, the Chief Scientist charged the SSC with developing a charter for a newly formed FDA Genomics Working Group.

2. **Intramural Challenge Grant Funding Programs:** To sharpen the focus and improve the quality and relevance of targeted regulatory science efforts, OCS, with the participation of SSC members and other subject matter experts, has established five intramural Challenge Grant funding programs: (1) Chief Scientist Challenges Grants, (2) the Office of Women's Health Challenge Grants, (3) the Office of Minority Health Challenge Grants, (4) the Medical Countermeasure Challenge Grants, and (5) the Nano Collaborative Opportunities for Research Excellence in Science (CORES) Grants. Developed as a unified submission system, these grant proposals must be first approved by each submitting center or office, and then reviewed by a peer review panel of subject matter experts before funding decisions are made. This process makes it possible for FDA offices to leverage the creative approaches of FDA investigators across the Agency to tackling their priority challenges.[13]

3. **Science Board Review of FDA's Regulatory Science Programs.** At the Chief Scientist's request, and in alignment with its recommendations, the Science Board has become increasingly engaged in programmatic reviews of FDA's product center and office regulatory science programs. Since 2007, the Science Board has conducted programmatic reviews within NCTR (2008), ORA—now part of OGROP (2008), CVM (2009), CFSAN (2009), the pharmacovigilance programs within CDER (2012), and CDRH (2013), and is currently reviewing CBER's postmarketing safety programs. Additionally, the Science Board has conducted reviews of several FDA programs, including ORA's Pesticide Program (2006), the National Antimicrobial Resistance Monitoring System (2007), and Global Health (2014).

[13] A similar process has been applied to peer review of external proposals solicited through RFAs.

4. **Program-specific changes.** In addition to organizational alignments and governance and review improvements within OCS, the component product centers and offices within FDA have been similarly repurposing existing resources, improving processes, and augmenting some programs to enhance the relevance and quality of their regulatory science efforts. A few examples of these quality improvements are:

   a. CDRH's recent report to the Science Board described an ongoing reorganization of its research structure, implementation of a new review process for proposed research projects, and a new programmatic review process, including the creation of the Regulatory Science Subcommittee of the Center Science Council to implement these efforts. Additionally, CDRH released its own report on regulatory science research.

   b. OFVM has centralized its scientific prioritization and project tracking. It has created a Science and Research Steering Committee (SRSC) that includes science and research leaders from the operating units of the FVM Program (CFSAN and CVM), as well as ORA, NCTR, OCS, and OIP.

   c. CDER has created a Science Prioritization and Review Committee that includes senior review and research leadership to identify and prioritize its science needs, develop a competitive proposal process to award Critical Path funding, and review proposals to address CDER needs.

   d. CBER has developed an improved method of conducting peer review of competitive research proposals. In 2012, CBER released its own Strategic Plan for Research and Regulatory Science.

   e. NCTR has added a new Division of Bioinformatics and Biostatistics, developed a pathway for input on its programs from the regulatory centers through its Science Advisory Board, and instituted a new process for center review of project proposals to ensure mission relevance. NCTR has also established a bio-imaging facility equipped with animal-sized instrumentation within the vivarium for FDA use; a specialized staff was recruited for operations.

   f. ORA has an ongoing program optimization initiative that will evaluate the current distribution of lab work to explore opportunities to shift or consolidate routine program work so as to create extra capacity that can be dedicated to developing new capabilities to expand FDA's regulatory method repertoire. Moreover, ORA shares a common database for research projects with CFSAN and CVM. Together with NCTR, the ORA Arkansas Regional Laboratory (ORA/ARL) has developed a Nanotechnology Core Facility (NanoCore) to ensure that FDA has the appropriate equipment, methods, and professional personnel to conduct these analyses in support of GLP toxicity studies for regulatory data gaps.

   g. CTP, the Center for Tobacco Products, is FDA's newest product center. Established in 2009, CTP is responsible for regulating the manufacture, marketing, and distribution of tobacco products to protect public health generally and to reduce tobacco use by minors. FDA's responsibilities under the law include setting product standards, reviewing premarket applications for new and modified risk tobacco products, requiring new warning labels, and establishing and enforcing advertising and promotion restrictions. FDA regulates tobacco products based on a public health

standard that considers both users and non-users of tobacco products. CTP has rapidly built a strong research program from the ground up that is designed to address key regulatory priorities, and leverages research capabilities with FDA (NCTR) and with Federal partners (NIH and CDC).

4. Enhance Resources and Infrastructure

The launch of the Critical Path Initiative, the Advancing Regulatory Science Initiative, and the release of the FDA Science Board's 2007 report focused attention on the need to enhance the regulatory science infrastructure and enterprise. Investments have supported intramural and extramural investigator-initiated projects that address targeted priorities and enabled FDA to build the infrastructure essential to support regulatory science efforts in emerging technology and emergency response.

The Critical Path Initiative. Funding for the Critical Path Initiative was authorized in the FDA Amendments Act of 2007. These funds, which were distributed to specific product centers and the Office of the Commissioner, have been applied largely to peer-reviewed competitive funding of intramural and extramural projects directed at improving knowledge, methods, and tools essential for the successful development of medical products.

The Medical Countermeasures initiative (MCMi). In 2010, FDA received one-time funding from the Department of Health and Human Services (HHS) to launch MCMi. These funds have been used to establish MCMi, including developing the MCMi infrastructure; hiring additional staff with expertise in MCMs; and supporting a broad range of MCM-related activities, including MCM regulatory science and professional development. Between FY 2012 and FY 2014, base resources were received to support MCMi.

Nanotechnology. In 2011, FDA received funds targeted at developing nanotechnology training, infrastructure, and research capabilities. With recommendations from the FDA Nanotechnology Task Force, the funds have supported training programs in nanotechnology manufacturing, characterization, and safety evaluation; built core nanotechnology research facilities; and developed a process for competitive review and funding of nanotechnology projects.

Generic Drug Regulatory Science Initiative. Establishment of the first user fee program for generic drugs in 2012 enabled the development of a robust program in regulatory science to support this area. While still under development, program priorities include research to improve postmarket generic drug surveillance; exploring methods for determining equivalence of locally acting and complex drugs; determining therapeutic equivalence evaluation standards; and developing computational and analytical tools needed to support all priority areas. The program is implementing its regulatory science plan through extramural and intramural research efforts.

Infrastructure Improvements

The FDA White Oak Campus. The continuing evolution of FDA's White Oak campus has created a vibrant scientific community that has increased cross-cutting opportunities for scientific collaboration and training. A newly completed South East quadrant houses CBER, CTP, and additional CDER laboratory and review components.

The Life Sciences Biodefense Laboratories (LSBL) is located in the South East quadrant of FDA's Consolidated White Oak campus. LSBL will house the CBER and CDER Office of Biotechnology Products research programs and an expanded vivarium, which represents a major investment in regulatory science infrastructure. Beginning occupancy in the summer of 2014 and eventually housing some 100 research programs, this large new laboratory complex provides FDA with a state-of-the-art facility to support a number of advanced technologies. They include:

- New *in vivo* imaging capability (MRI, digital X-ray, etc.)
- *In vitro* imaging (high resolution confocal microscopy, TEM)
- A dedicated transgenic derivation facility
- Expanded space to support NGS and associated bioinformatics/IT infrastructure (dedicated computer room)
- Multi-color flow cytometry, and high resolution structural biology (mass spectrometry and NMR)
- Significantly expanded BSL-3 capacity, with a total of 10 BSL-3 suites, including a core BSL-3 suite for flow cytometry and confocal microscopy, BSL-3 insectarium, and several agent-specific BSL-3 suites with animal holding capacity
- A BSL-2 insectarium for working with the causative agent of malaria
- Common space on each floor of the facility to house additional technology-specific needs, such as PCR rooms, microarray, and histology

Highly Integrated Virtual Environment, HIVE. To prepare for the regulatory application of next-generation sequencing (NGS), FDA has leveraged the High Performance Computing (HPC) facility to develop the IT infrastructure to support data storage, transfer, and analytics that are unique to this new technology. Using funding from MCMi, CBER has assembled a team of IT professionals, including significant bioinformatics expertise, to develop tailor-made software analytics to support FDA's regulatory science program. HIVE is needed to evaluate this new technology and FDA is moving toward developing a production platform that can be used to house and analyze NGS data that sponsors provide as part of formal regulatory submissions.

CFSAN Wiley Data Center. Large-scale fields such as genomics have created a need for computational and data transfer capabilities that exceed the normal desktop workstation. In conjunction with OIM, FDA\CFSAN (College Park headquarters) and FDA\ORA are collaborating to build the required IT infrastructure to support the use of whole genome sequencing across FDA's field laboratories and its integration with compliance/enforcement activities of FVM. Additionally, FDA is engaged with other HHS partners, including the National Center for Biotechnology Information (NCBI) at NIH and CDC to ensure that WGS data are useable and comparable across different HHS departments.

CDRH High Performance Computing (HPC) Environment. The HPC provides a massive computational cluster (3168 processing cores in 356 nodes) for scientists in all FDA centers to use in their research and regulatory work. Characteristic applications undertaken with the HPC include large-scale modeling and simulations, genomic analysis, computational physics, molecular and fluid dynamics, Bayesian analysis, semantic data mining, and many others job types that overwhelm the capacity of even the most powerful scientific workstations. The HPC hosts numerous high-quality, open-source scientific applications used for past and ongoing projects and two genomic pipeline frameworks, the CLC Genomics Workbench and CBER's HIVE.

Janus Clinical Trials Repository: The Janus Clinical Trials Repository (CTR) development project entails development, implementation, and deployment of a data warehouse application to enable the reliable validation, transformation, loading, and management of standardized clinical trials data in a secure database, and to support reviewer access to that data using a variety of analysis tools such as JReview, JMP, and others. The CTR is being developed by FDA in collaboration with the National Cancer Institute (NCI) through an Interagency agreement under the auspices of the FDA/NCI Interagency Oncology Task Force. CTR development and implementation was done at NCI. Currently, FDA is working with NCI to complete the transition of the CTR application to full production operation at FDA's White Oak Data Center (WODC).

Nanotechnology Core Facilities. Nanotechnology Core Facilities located in Arkansas (NCTR/ORS) and the White-Oak campus provide FDA's laboratory testing capacity. In line with FDA's Nanotechnology Task Force report of July 2007, top-tier priorities are:

- Developing testing methods to assess the quality, effectiveness, and safety of products that use nanomaterials (including their stability and interaction with biological systems)
- Developing standards to be incorporated into the safety assessment of products that contain nanomaterials or otherwise involve the application of nanotechnology

Cross-Cutting Instrumentation and Facilities. In addition to the examples above, recent regulatory science initiatives have enabled FDA to improve the instrumentation in many areas, including installation of next-generation sequencers in FDA field laboratories for rapid identification of pathogens; and expanded use of LC-MS/MS, high-field NMR, and a number of other spectroscopic instruments—both laboratory and hand-held—to greatly improve the analytical capabilities needed for rapid and detailed characterization of regulated products, ingredients, and contaminants. FDA has established facilities to study manufacturing of complex biologics and drug formulations, non-invasive imaging, and for maintenance of special animal models, such as humanized mice (mice that carry partial or complete human physiological systems).

5. Develop New Mechanisms and Programs to Leverage External Expertise

To keep pace with advances in technology, FDA has accelerated efforts to develop new approaches to engaging in synergistic collaborations with other governmental agencies, academia, industry, patient organizations, professional societies, and other stakeholders.

At the same time, FDA has expanded its use of existing mechanisms to develop new collaborative programs. FDA partnerships are structured to uphold the principles of transparency, fairness, inclusiveness, scientific rigor, and compliance with Federal laws and FDA policy. Examples follow.

Public–Private Partnerships (PPP). Recognizing that challenges in regulatory science often require a broader, collective effort, a provision was included in FDAAA for a new entity, the public–private partnership (PPP). PPPs are used to create, implement, and manage strategic scientific partnerships to support FDA's public health mission. These partnerships leverage intellectual capital, infrastructure, and in-kind and financial resources to facilitate successful implementation of programs that are typically of a magnitude and scope beyond the capabilities of a single entity. PPPs enable FDA to partner with a wide range of entities, including industry, academia, non-profit organizations, and other governmental agencies. PPPs aim to improve the public health by enabling FDA to participate in and provide guidance to science-driven alliances with other organizations to implement public health goals.

Partnership Intermediary Agreements (PIA). The PIA is an agreement between the government and an intermediary organization such as State and local governmental agencies and nonprofit entities operated by or on behalf of a State or local government. The goal is to perform partnership intermediary services of mutual interest. PAIs enable FDA to participate in joint activities that increase the likelihood of small businesses and educational institutions studies that can benefit from a Federal laboratory's knowledge and technology-related assistance. In 2011, FDA entered into a memorandum of understanding (MOU) with the State of Arkansas to establish an Arkansas Center of Excellence in Regulatory Science to cooperate in educational programs. As a result of the MOU, a PIA was signed between FDA and the Arkansas Research Alliance to organize the physics, engineering, ecology, and pharmacology expertise of advanced degree-granting institutions and FDA's toxicology expertise. The aim is to develop standards for purity, analysis, detection of characterization of carbon-based nanomaterials, and their effects on human and environmental health.

Centers of Excellence in Regulatory Science and Innovation (CERSI). A strong in-house contingent of scientific and technical experts proficient in cutting-edge science and technologies, together with a network of collaborations is key to FDA's capacity to evaluate increasingly complex products and promote innovation that addresses unmet public health needs. To this end, building on previous FDA extramural programs, in 2011 FDA launched the Centers of Excellence in Regulatory Science and Innovation (CERSIs) with initial programs at Georgetown University and the University of Maryland. The CERSIs promote cross-disciplinary regulatory science training, scientific exchanges, and research. In 2014, the Johns Hopkins University and UC-San Francisco (UCSF)-Stanford University CERSIs were launched, bringing the number of FDA CERSIs to four, with six academic institutions involved.

The Broad Agency Announcement (BAA). The BAA is a mechanism under FDA's Program for Extramural Regulatory Science and Innovation (PERSI) for soliciting creative external proposals that address broad challenges facing FDA. The BAA outlines research areas of interest that will help fulfill FDA requirements in technology, materials, processes, methods, devices, or techniques in specific topics. Unlike the contract RFP process that specifies milestones and deliverables, the BAA identifies the regulatory science challenge, leaving the proposer to design the specific approach to solving it. This mechanism enables FDA to better understand the breath of innovative scientific and technical solutions available to solve difficult problems.

Network of Experts. Developed by CDRH, the Network of Experts is a vetted network of outside scientists, clinicians, and engineers who can provide FDA staff with rapid access to scientific, engineering, and medical expertise when it is needed to supplement existing knowledge and expertise within the Agency. This program is designed to broaden FDA exposure to scientific viewpoints, but not to provide external policy advice, consensus, or opinions. This mechanism enables FDA scientists to gain further scientific understanding of new and emerging fields of science and pioneering technologies.

Fellowship Programs. FDA has actively expanded its opportunities for fellowships in the past several years. Building on the success of the ongoing Interagency Oncology Task Force Joint Fellowship Program (IOTF) with NIH, FDA has launched the Commissioner's Fellowship Program, as well as a provided a number of other fellowship and internship opportunities targeted for different levels of education and experience .

Reagan-Udall Foundation. Establishment of the Reagan Udall Foundation for FDA (RUF) was authorized in FDAAA. The core operations include Promoting Safety and Better Evidence, Improving Regulatory Science Processes, and Building Scientific Capacity. RUF has engaged with FDA in a number of projects of importance, including the Innovation in Medical Evidence Development (IMEDS) program, which is focused on improving postmarket surveillance. The RUF also launched the Alzheimer's Disease Regulatory Science Fellowship as part of a pilot program to expand fellowship opportunities in critical areas. Recently, RUF and the FDA Food and Feed Program began a collaboration to develop the Food Safety Innovation Consortium. This will be a new public-private partnership between academia, industry, and government to advance regulatory science in the food safety arena.

In summary, FDA has recognized the increasing importance of regulatory science programs for guiding scientifically sound regulatory decisions and actions. With congressional support, FDA has defined and implemented an aggressive program to strengthen the basic building blocks to create a robust foundation that will support regulatory science programs and projects.

FDA Partnership in Action: The Deepwater Horizon Oil Spill of May 2, 2011

The Deepwater Horizon oil spill on May 2, 2011, was an emergency for millions of Americans who relied on seafood harvested in the Gulf of Mexico. It threatened coastal communities with enormous economic losses due to widespread fear of contamination.

Immediately after the spill began, FDA worked with the National Oceanic and Atmospheric Administration (NOAA) and the affected States to ensure that appropriate closures were put in place and to define the conditions under which waters that were closed could re-open. In partnership with NOAA, FDA inspectors analyzed thousands of samples from the huge variety of marine life that is commercially harvested from Gulf waters for polycyclic aromatic hydrocarbons (PAH) and toxic oil dispersants.

At the outset of the oil spill, the existing reference test for PAHs (the primary contaminant of concern in oil) took five to seven days to obtain results. Given the urgent need for testing large numbers of seafood samples as quickly as possible and to make timely re-opening determinations, FDA worked aggressively to develop a reliable and accurate alternative test that reduced analysis time from more than a week to 48 hours.

Working in the framework of the science-based regulations of the seafood Hazard Analysis Critical Control Points (HACCP) Program, FDA also conducted hundreds of inspections of seafood processors in the Gulf region to verify that processors received fish harvested only from waters from which harvesting was permitted. Only after all samples collected from an area passed both sensory and chemical testing was a harvest area allowed to reopen based on the standard protocol that FDA and NOAA had developed with the States.

To further ensure the public health, NOAA and FDA conducted additional studies to verify that dispersants had not accumulated in tissues of fish and shellfish. FDA enhanced its ability to test for these toxic chemicals by working with NOAA to develop a practical, efficient, and reliable test for their presence in edible portions of seafood that could be deployed in Federal and State labs. FDA's swift, collaborative, and science-based response to the Gulf of Mexico oil spill served to protect Americans while effectively minimizing the negative economic impacts on Gulf seafood producers and exporters.

Section B. Strengthen and Leverage Human & Capital Resources

1. Secure Critical Scientific Capability and Capacity

FDA's scientific reviewers and researchers are critical to fulfilling our public health and regulatory mission. Their pivotal role is most clearly underscored by the fact that FDA-regulated products account for about 20 cents of every dollar spent by American consumers. FDA must recruit top scientists, train them in law and regulatory policy, ensure that they stay current with the latest scientific knowledge, and retain them through promotional and achievement award mechanisms.

Since the 2007 *FDA Science and Mission at Risk* report, FDA has undertaken significant initiatives to promote a culture of scientific excellence. As described in Section A, FDA has established the Office of Scientific Professional Development to strengthen scientific recruitment, augment training and development opportunities, and improve retention activities.

2. Recruit Top Scientific Talent to FDA

Because science is at the core of everything we do at FDA, recruiting outstanding scientists is essential to the success of our mission. A general paucity of training in, and exposure to, regulatory science in most scientific and medical professional curricula means there is a limited pool of potential candidates with appropriate training, experience, and expertise to fill FDA positions. It is therefore critical that mechanisms be put in place to recruit scientists and medical professionals with the needed expertise while developing new opportunities for training younger scientists in regulatory science. The training efforts increase the pool of qualified candidates for FDA positions while augmenting the availability of scientists trained in regulatory science among stakeholder organizations, industry, and academia.

In addition to hiring scientists into career General Schedules positions, FDA employs several recruitment and hiring options. For example, the Title 42 hiring mechanism enables FDA to attract staff with critical scientific and technical skills at pay levels more commensurate with academia and the private sector. The Title 38 Market Pay program similarly enables medical officers and dentists to receive salary and hiring incentives comparable to those outside of government. Additionally, the Office of Personnel Management (OPM) gives FDA *Direct-Hire Authority* to fill vacancies when a critical hiring need or severe shortage of candidates exists.

The Senior Biomedical Research Service (SBRS) is also used to recruit and retain the most outstanding research and review scientists. Because the number of SBRS positions available to FDA is limited, scientists are proposed for membership only when they meet the rigorous criteria delineated in SBRS Policies and Procedures and if the flexibilities of other senior-level personnel systems are insufficient to meet FDA's recruitment and retention needs.

FDA also collaborates with external organizations through the Intergovernmental Personnel Act, which provides a mechanism for visiting academic scientists to work at FDA for short-term assignments up to two years. During this time, visiting academic scientists provide their knowledge and expertise while collaborating with FDA scientists.

Attract New Talent: Expand FDA Fellowship and Internship Opportunities

Although attracting top scientific talent is a priority, FDA also recognizes the need to recruit and train younger scientists who may not normally consider FDA as a career option. In the past few years, the Agency has introduced new fellowship and student programs to attract scientists and train them. FDA trains them in regulatory science, law, and policy while exposing them to the range of FDA career opportunities.

At the Agency level, the two-year Commissioner's Fellowship Program, managed by OSPD, introduces outstanding early career scientists to FDA through the completion of a regulatory science project and formal courses. Fostering succession planning, this Fellowship program identifies regulatory science priority areas to which the Fellows apply. From the program's inauguration in 2008 to 2014 there have been 182 graduates, with 76% remaining at FDA upon graduation.

The Commissioner's Fellowship Program

I came to the program seeking experience in the drug development process from the unique perspective that only FDA can offer. As a clinician with training in pediatrics, I was interested in the regulatory and scientific considerations that are pertinent when developing drugs and biologics to treat diseases and conditions affecting newborns, infants, children, and adolescents. The program gave me a comprehensive understanding of how all of FDA's components work together toward the goal of promoting and protecting the public's health. **Dionna Green, M.D., former Commissioner's Fellow, currently Medical Officer in FDA's Center for Drug Evaluation and Research**

After completing my Ph.D. in Food Science and Technology, I was interested in pursuing research at a government institution. The CFP position provided me with the opportunity to apply my research abilities to FDA's mission of protecting and promoting public health. During my time as a Fellow, I contributed to developing laboratory protocols related to food safety testing, published a number of research studies on these topics, and presented this research at scientific meetings. In addition, I built a strong network of contacts with whom I continue to collaborate in my current position as a tenure-track faculty member of Chapman University. **Rosalee S. Hellberg, Ph.D. former Fellow, currently Assistant Professor, Food Science at Chapman University**

Product center-specific fellowship programs for post-graduates have also been developed, such as CDRH's Medical Device Fellowship Program, which is designed to bring on critical skills for a finite period of time as device technology trends evolve. CTP's Tobacco Regulatory Science Fellowship is another example. These programs introduce scientists to the center's regulatory research and activities to

stimulate their capacity to conduct and support regulatory science outside of government and to foster interest in seeking permanent employment at FDA.

An important and flexible mechanism FDA employs to enhance training opportunities is the Oak Ridge Institute for Science and Education (ORISE) Fellowship Program. Managed through an interagency agreement with the Department of Energy, this program offers a straightforward mechanism for bringing on pre- and post-doctoral fellows to work on specific regulatory science projects for a defined period of time. It enables FDA scientists who have received funding through one of the intramural competitive funding programs to quickly bring on qualified candidates to conduct the research. Thus, this program aligns fellowship resources with projects deemed to be the most scientifically important and relevant by the peer review process. New initiatives outlined in Section A, like the Critical Path Initiative and MCMi, have enabled hundreds of ORISE fellows to participate in important regulatory science research projects over the last five years.

The Agency-wide InterAgency Oncology Task Force (IOTF) Fellowship is an ongoing collaborative program with the National Cancer Institute to train a cadre of scientists in regulatory review and research. Since 2005, 39 IOTF Fellows have completed the program, with 51% remaining at FDA upon program completion.

In addition to fellowship programs, FDA has also expanded the number of internship opportunities for students in a wide variety of disciplines, including veterinary medicine, pharmacy, and engineering. Typically of shorter duration, these internships are often integrated into a graduate or professional curriculum.

Raising awareness of regulatory science career opportunities at academic institutions is crucial to attracting top-tier scientists to FDA. The Agency hosts a number of student and fellowship visits from academic institutions, such as George Washington University, Harvard, the University of Chicago, and Yale.

3. Enhance FDA Scientific Training and Continuing Education Opportunities

Once a scientist is selected, FDA invests significant resources in orientation and providing cutting-edge scientific training. Centers conduct orientation programs that integrate law, science, and regulatory policy so that the scientist has the foundation to make regulatory decisions. These competency-based orientation programs include courses on statutes, regulations, guidance, and policy and are complemented with product center mentoring programs for on-the-job training. FDA also sponsors continuing education for human and veterinary clinical staff.

From the moment that scientists come on board at FDA, every effort is made to ensure their continual assimilation of the latest developments in science.

New science, such as whole genome sequencing, stem cell markers, chemical hazards, modeling, simulation, systems biology, nanotechnology, and imaging is constantly changing, and FDA strives to keep staff current by:

- Providing center staff training and education programs
- Sponsoring FDA-wide courses, lectures, and seminars with scientific thought leaders
- Building cross-Agency collaborations
- Supporting staff attendance at educational programs and professional scientific and clinical meetings outside FDA
- Expanding intramural and extramural collaborations

At the center level, a number of courses and workshops and center seminars, rounds, and lectures exist that address the science specific to tobacco, drugs, biologics, devices, food safety, or veterinary medicine. Many of these courses and workshops invite external scientific experts. Center staff also have the chance to participate in external site visit programs such as CBER's Regulatory Site Visit Program and CDRH's Experiential Learning Program, which provide FDA staff with real-world knowledge learning from industry, academia, or the clinical community.

Centers also collaborate to sponsor scientific courses workshops, seminars, and lectures such as CFSAN's and ORA's Field IQ Program, the CBER, CDER, and CDRH Bone Regenerative Medicine Workshop, and the NCTR and CBER Science Training and Exchange Program. Additionally, centers collaborate to provide hands-on training with opportunities through the NCTR-ORA and White Oak NanoCore Facilities as well as the Foods and Veterinary Medicine Whole Genome Sequencing Training Center. Collaborations occur within product centers, such as CDRH's cross training initiative with staff in research labs that are completing a temporary assignment in review divisions.

At the Agency level, there are multiple working groups that address regulatory science training priorities:

- **The Nanotechnology Taskforce**: Sponsors courses and hands-on training
- **MCMi**: Sponsors MCMi professional development activities with lectures, conference support, and briefings to ensure that FDA scientists are fully aware of the threats and risk as they conduct benefit-risk analyses on MCMs
- **The Committee for the Advancement of FDA Science**: Sponsors the Chief Scientist Distinguished Lectureship series, which brings in international and national scientific experts

Centers and offices share scientific training opportunities through an Agency-wide FDA Scientific Professional Development Calendar.

FDA also collaborates with external organizations to address scientific professional development. The Agency sponsors a number of public workshops, inviting scientific experts in the academic community, industry, other Federal agencies, international regulatory bodies, and the general public to discuss scientific developments and their impact on regulatory science.

At the product center and Agency level there are a number of co-sponsored educational events, such as FDA's collaboration with Health Resource Alliance to present the New Frontiers in Science Distinguished Lectureship series that fosters expert scientific exchange between FDA and the scientific community. Scientific experts visit FDA for one to three days to present a lecture or seminar and discuss cutting-edge scientific issues. FDA is also collaborating with the CERSIs to address scientific training needs through co-sponsored lectures and conferences.

FDA staff and the scientific community participate in personnel exchanges such as those under an academic memorandum of understanding. Visiting scientists have the opportunity to collaborate with FDA staff and share their scientific expertise while FDA staff have the chance to participate in professional development, conducting research or clinical care at an external institution. This opportunity is important to maintaining their knowledge and skills.

4. Promote a Culture of Scientific Excellence: Peer Review and Recognition

FDA allocates substantial resources to recruit, train, and develop scientific staff. We also recognize that rewarding and promoting staff are essential to retaining top scientists.

For over three decades, FDA's competitive Peer Review Program, composed of scientific subject matter experts and human resource specialists, has supported FDA's recruitment and promotion activities. The program ensures that FDA retains a top-tier scientific workforce that can apply the latest technology and science-based standards to the regulatory challenges presented by new FDA-regulated products.

FDA has two Agency-wide Peer Review Committees for the Medical Officer and the Regulatory Review Scientist, and seven Research Scientist Peer Review Committees. Recently, FDA established Master Reviewer Peer Review committees at product centers.

FDA also honors scientists who have made outstanding contributions with Scientific Achievement Awards. Granted yearly in 10 categories, FDA added a Lifetime Achievement Award in 2013. The nominations are reviewed by an Agency-wide committee with final selections made by FDA's Science Board.

5. Build Intramural Collaborations

Expanding collaborative efforts, both within and external to FDA is critical for the success of regulatory science. Emerging technologies often are incorporated into a range of FDA-regulated products. A multidisciplinary approach and cross-cutting cooperation and collaboration are key to identifying emerging scientific issues and offering practical and scalable solutions.

Cross-center collaborations, such as the ORA/CDRH Strategic and Scientific Compliance collaboration to focus laboratory analytical and field examination work on high-risk and high-priority medical devices and radiation emitting products, are common. Large FDA-wide programs that involve multiple centers, like the Sentinel Initiative, also require collaborative approaches to issues like methods development and validation. It is expected that consolidation of centers at the White Oak campus, which presents more opportunities for interaction, will increase these collaborations.

As mentioned in Section A, the introduction of centralized competitive funding programs within OCS has offered a platform for cross-center collaborations. These types of cross-center collaborations are especially important in light of the increased prevalence of products that combine elements regulated by different centers. For example, a Chief Scientist Challenge grant was awarded to scientists at CDRH and CDER to study novel *in vitro* electrophysiological approaches to measure the effects of drugs substances on human cardiac contractility—a safety issue considered in human drug trials using device technologies regulated by CDRH.

The Senior Science Council provides an important inter-center nexus for discussions of emerging technologies and scientific issues. To facilitate these discussions, a number of working groups have been formed. Examples follow:

- **The Genomics Working Group**: FDA launched the FDA Genomic Working Group in anticipation of future regulatory submissions that include next generation sequencing (NGS) and to generate the ability to develop the tools to evaluate such data. This group is ensuring FDA readiness to address IT and scientific challenges and for NGS data submission, including (1) how to store, transfer, and perform efficient computation on large and complex NGS data sets; (2) how to assess bioinformatics needs, expertise, and resources; (3) how to evaluate data quality and data interpretation for regulatory decision-making. The working group includes representatives from each FDA Center, Office of Chief Scientist, Senior Science Council, and the Science Computational Board

- **Nanotechnology Task Force (NTF):** A critical role of the NTF, which coordinates its activities with the National Nanotechnology Initiative, has been to ensure that FDA regulatory scientists—review, research, field, and regulatory policy staff—are equipped to deal with the introduction of nanoscale materials in drugs, biologics, food, cosmetics, devices, and other FDA-regulated products. FDA has sponsored several hands-on laboratory courses, some in collaboration with the National Cancer Institute's Nanotechnology Characterization Laboratory, to acquaint these key personnel with the latest developments in nanotechnology manufacturing processes and general principles of the interaction of these materials with biological systems. Through the Collaborative Opportunities for Research Excellence in Science (CORES) Program, the scientific research priorities identified by the task force, such as defining physicochemical characteristics of nanomaterials that affect potency and safety, the pharmacokinetics of products containing nanomaterials, and the safety of specific nanoparticles can be addressed.

6. Leverage External Capabilities to Advance Regulatory Science

To obtain the regulatory science research needed to support our broad and diverse regulatory mission, FDA uses a combination of approaches:

1. A robust intramural program
2. Engagement in technology transfer and collaborative research with the external scientific and medical communities

3. Formal external partnering mechanisms
4. An FDA-funded extramural regulatory science program

As mentioned previously, since 2007, several new mechanisms have been added to FDA's arsenal to increase our ability to leverage external expertise, including PPPs, a Regulatory Science BAA, and CERSIs. Although not detailed in this report, it is important to note that a primary source of external input on scientific issues related to regulatory decisions is through the use of FDA's 50 advisory committees and panels to obtain independent expert advice on scientific, technical, and policy matters.

FDA Investigator-Initiated Collaborations

FDA scientists routinely collaborate on an individual basis with non-FDA colleagues. These collaborations use a number of legally mandated and approved technology transfer mechanisms to leverage external expertise, such as Material Transfer Agreements, Confidential Disclosure Agreements, Cooperative Research and Development Agreements (CRADAs), and applying for patents and licensing of inventions to external partners. More recently, FDA has also used research collaboration agreements (RCA) to frame collaborations that involve exchange of reagents, data, and intellectual input, but do not involve receipt of financial support for the collaboration from the external collaborator. The RCA was developed and implemented in 2009 to enhance FDA researchers' ability to put together collaborations with low probability of intellectual property potential, geared toward more basic science work and leading to scientific publication as a usual outcome. The RCA was designed to help FDA scientists who expressed a need for a leveraging mechanism more appropriate for smaller-scale collaborations. In all cases, FDA reviews external collaborations, especially those with regulated industry partners, for conflict of interest.

Together, these agreements provide the legal framework and protections to allow our intramural scientists to engage in collaborations with external scientists in other governmental agencies, academia, and industry. These agreements extend our collective scientific expertise and access to research tools and data.

Formal External Partnering Programs

FDA interacts broadly, with colleagues in academia, government, non-profit organizations, and industry, as appropriate, to leverage expertise and resources not available in house. Important examples include:

Postmarket Surveillance. Monitoring real-world use and safety of FDA-regulated products has historically been based in part on passive postmarket reporting. Although this approach has proven useful for detecting serious and rare adverse events, there is a need to complement this approach with active surveillance approaches that leverage multiple external resources, applying innovative methods of monitoring FDA-regulated products that will enhance public health in ways previously unachievable. The following examples illustrate FDA's approach:

- **The Sentinel Initiative**

Section 905 of FDAAA mandated FDA to use *active surveillance* to monitor the safety of drugs after licensure for marketing. To meet this requirement, FDA has implemented the Sentinel Initiative, an

effort to build and implement a new active surveillance system that will eventually be used to monitor all FDA-regulated products throughout their lifecycle. Thus far, the Mini-Sentinel Pilot has leveraged electronic health care records from over 150 million patients across 18 data partners to support hundreds of queries related to surveillance of postmarket medical product safety and use.

FDA continues to leverage external expertise and data to conduct ongoing epidemiological studies related to FDA-regulated products. Partners include academic centers, large health-care networks, like Kaiser and Pilgrim Health, as well as Federal partners such as the Veterans Administration, Department of Defense, and Centers for Medicare & Medicaid Services. In addition, FDA accesses a number of private and public data sources, including prescription data, medical records data, and emergency room admissions data.

- **The Reagan-Udall Foundation** for FDA

RUF has launched the Innovation in Medical Evidence Development and Surveillance (IMEDS) program. IMEDS is a program within the Reagan-Udall Foundation that supports the Sentinel Initiative by initiating and facilitating research into the methods of safety evaluation in large databases. Building on results of the Observational Medical Outcomes Partnership, IMEDS-Methods aims to improve the tools for conducting post-marketing safety surveillance using automated health care data and to foster the adoption of its findings.

- **The National Postmarket Surveillance Plan** for medical devices

This is FDA's vision for medical device postmarket surveillance: the creation of a national system that communicates timely, accurate, systematic, and prioritized assessments of devices throughout their marketed life, using high-quality, standardized, structured, electronic health-related data; operates in near real-time using a variety of privacy-protected data sources; reduces the burdens and costs of medical device postmarket surveillance; and facilitates the clearance and approval of new devices, or new uses of existing devices.

The Generic Drug User Fee Regulatory Science Program, launched in 2013, outlines a number of important regulatory research priorities for generic drugs. The program has a large portfolio of extramural grants and contracts (19 awarded in FY 2013) that leverage external expertise to address the research priorities.

CFSAN is actively involved in high-visibility endeavors with several academic institutions through its Centers of Excellence (COE) program. These collaborations yield critical information that enhances on-going efforts to protect the food supply. CFSAN has four COEs, the National Center for Food Safety and Technology (NCFST) with the Illinois Institute of Technology; the Joint Institute for Food Safety and Applied Nutrition (JIFSAN) with the University of Maryland; the FDA COE for Botanical Dietary Supplement Research at the National Center for Natural Products Research (NCNPR), University of Mississippi; and the Western Center for Food Safety (WCFS) with the University of California at UC, Davis. Moreover, formal agreements with the states for conducting inspections enhance the Center's ability to meet its public health mission.

The Patient-Focused Drug Development Initiative[14] helps provide a more systematic approach for FDA to obtain patient input on specific disease areas, including patients' perspectives on their condition, its impact on daily life, and available therapies. FDA sees Patient-Focused Drug Development as an important enhancement to our current mechanisms for getting patient input, such as advisory committee meetings, which are often within the context of one specific new drug application. Patients who live with a disease have a direct stake in the outcome of FDA's regulatory decisions and are in a unique position to contribute to the understanding of their disease. FDA is committed to obtaining patient perspectives on 20 disease areas during the next couple of years.

The Patient Preference Initiative builds on guidance to understand the key factors to consider when making benefit–risk determinations for certain medical devices. Importantly, it discusses developing patient-centric metrics to measure benefit and ways of measuring a patient's tolerance for risks and preference in benefits. The initiative aims to incorporate patient perspectives on the benefit–risk trade-offs of medical devices into the full spectrum of regulatory processes, to inform medical device innovation by the larger medical device community, and to advance the science of how best to measure medical device preferences among patients, caregivers, and providers.

A CDRH sponsored patient-centric study of benefit-risk preferences among obesity patients demonstrated that high-quality quantitative data can be elicited from patients using robust methods. The data from this study were considered in the recent approval of a new weight loss device and have informed clinical trial design for novel devices to treat obesity.

FDA issued a draft guidance in May 2015 that builds on a previously issued guidance to provide further information to stakeholders (industry, patient groups, and academia) about how to collect and submit patient preference information that can be used by FDA staff when making benefit-risk determinations in the premarket review of certain medical devices. FDA is partnering with the Medical Device Innovation Consortium, who released a framework for collecting patient preference data and a catalog of methodologies to elicit patient preference in May 2015.

Public–Private Partnerships (PPPs) and Consortia

In the past five years, FDA has formalized its approach to engaging in PPPs, due to new authority under the FDA Amendments Act (FDAAA), passed in 2007, authorizing FDA to engage with PPPs to address focused problems that require a coordinated, multi-sector, multi-disciplinary approach. PPPs are increasingly acting as neutral third parties to manage consortia, an increasingly used model of collaboration. Indeed, in part as a result of discussions with FDA and other organizations, the organization Faster Cures has recently launched its Consortia-pedia, "to better understand the breadth and scope of approaches that a wide range of consortia have adopted to bring together non-traditional partners with a shared R&D goal."[15]

[14] It is part of FDA's performance commitments accompanying the fifth authorization of the Prescription Drug User Fee Act (PDUFA V).

[15] Available at: http://fastercures.org/assets/Uploads/45700-ConsortiaReport.pdf. Accessed on May 20, 2014.

FDA's role in consortia is to provide general information on regulatory processes and requirements to help focus the work of the consortia on addressing regulatory science issues germane to FDA's public health mission. FDA is engaged in a large number of consortia — more than 15 in CDER alone. The consortia provide opportunities to make significant progress in very specific areas, since they tend to have a narrow focus and clearly defined objectives. Below are a few examples of consortia activities and outcomes.

- **Medical Device Innovation Consortium (MDIC).** The MDIC is a groundbreaking consortium of more than 40 members, with broad representation by private industry (both large and small companies), non-profit organizations (e.g., Pew, Patient-Centered Outcomes Research Institute), patient advocacy organizations (i.e., the National Organization for Rare Disorders and Faster Cures), as well as other governmental agencies (i.e., NIH, CMS). The MDIC augments FDA's regulatory science expertise through collaborations on projects that foster innovation and bring novel products to market. Projects have been initiated with broad engagement from all stakeholders that are focused on (1) clinical trial innovation that will simplify trials and accelerate access to breakthrough technologies, (2) developing a framework for incorporating patient preferences into the assessment process, (3) expanding the use of regulatory grade computer models and simulations to increase the confidence in device safety and efficacy, and (4) identifying methodologies to improve the overall quality of medical devices.

- **Medical Device Epidemiology Network (MDEpiNet).** MDEpiNet provides global leadership in innovative data source development and analytic methodologies to enhance regulatory science applied to medical device research and surveillance. FDA is collaborating with a professional organization, academic centers, and industry on the MDEpiNet PPP. MDEpiNet aims to develop new ways to study medical devices that improve the understanding of their safety and effectiveness throughout their life cycle.

- **MicroArray Quality Control Consortium (MAQC).** The MAQC, NCTR-initiated and managed, is a partnership of scientists from FDA product centers, regulatory organizations of Federal and foreign governments, academia, and industry. The consortium's goal (now in phase MAQC III or SEQC) was to explore and establish procedures of performance, organization/presentation, and analysis of data obtained from microarray-based procedures for use in regulatory decisions and to translate these into best-practices and guidance documents for new product applications. To date, publications have been completed for the performance and analysis while the investigations of SEQC ("NexGen") technologies is ongoing.

- **Biomarkers Consortium (BC).** The consortium, managed by the Foundation for National Institutes of Health, includes FDA, CMS, NIH, and a combination of non-profit organizations, including patient advocacy organizations and professional associations (17 to date) and for-profit companies (15 to date). The shared goal of this broad spectrum of stakeholders is to identify, develop, and qualify potential high-impact biomarkers to enable improvements in drug development, clinical care, and regulatory decision-making. The BC has launched nine projects in areas such as metabolic disorders, Alzheimer's disease, lung cancer, and lymphoma and completed one project that tested and

confirmed the protein adiponectin as an important biomarker in monitoring one facet of treatment in Type II diabetes.

- **Coalition Against Major Disease (CAMD) Consortium**, managed by the Critical Path Institute, aims to develop new biomarkers, common data standards, integrated databases for clinical trial data, and quantitative model-based tools to facilitate development of new treatments for neurodegenerative diseases, such as Alzheimer's and Parkinson's disease. Recent projects have resulted in a qualification opinion with European Medicines Agency (EMA) for the use of low baseline hippocampal volume for patient enrichment in pre-dementia trials, as well as positive regulatory decisions from FDA and EMA for the use of a clinical trial simulation tool to aid in trials for mild to moderate stages of Alzheimer's Disease.

Office of the Chief Scientist's Extramural Regulatory Science Program

One of the new efforts FDA has initiated (mentioned in Section A) is the Program for Extramural Regulatory Science (PERSI), which uses grants and contracts to address targeted priorities.

- **Program in Extramural Regulatory Science (PERSI)**. In May 2012, FDA issued its first BAA to solicit proposals to use FDA funding to support regulatory science and innovation in the extramural community. The BAA fulfills an FDA requirement to use or leverage academic and industry capabilities to advance the state of the art and achieve improvements in technology, materials, processes, methods, devices, or techniques (especially for innovative or emerging concepts and technologies of which FDA has limited expertise or capacities). The BAA includes the eight priority areas identified in FDA's Strategic Plan for Regulatory Science as well as a new area added in 2013, *Strengthening the Global Product Safety Net*. Since 2012, a total of 48 contracts have been awarded.

  A few examples of notable projects funded through the BAA are provided here.

  Epidemico was funded to explore the potential of social media data mining, using natural language processing combined with crowdsourcing, to validate the usefulness of user-generated digital data in postmarket surveillance in real-time. Twitter, Facebook, and web sites are used to generate visualization of results showing temporal, geographic, and source analyses.

  In 2013, two new projects were funded to develop improved non-clinical models for predicting clinical outcomes. **Auckland Bioengineering Institute** received funding to develop an anatomical and functional population model of the human musculoskeletal system to generate accurate, volumetric meshes of muscles and bones of the lower limb, using statistical shape models extracted from a large dataset with open-source software. And **Harvard University's Wyss Institute for Biologically Inspired Engineering** received funding to extend their Organs on Chips technology to develop models of radiation damage in the lung, gut, and bone marrow that could be used to evaluate candidate medical countermeasures for acute radiation syndrome.

Centers for Excellence in Regulatory Science and Innovation. To support regulatory science in academia, FDA has implemented funding for Centers of Excellence in Regulatory Science and Innovation. In October 2011, the first two CERSIs were awarded: CERSI University of Maryland and CERSI Georgetown University. Two additional CERSI awards were granted in 2014 to the University of California San Francisco/Stanford and Johns Hopkins University. FDA-funded CERSIs have promoted regulatory science in three ways.

1. Provide cross-disciplinary regulatory science training by facilitating development of new educational programs. University of Maryland has developed an MS in Regulatory Science curriculum, and Georgetown University offers a unique concentration in regulatory science as part of the Master of Science in Clinical and Translational Research. The CERSI centers have engaged students beyond the degree programs, sponsoring small student projects and regulatory science competitions.

2. Sponsor seminars, workshops and conferences to enhance professional development opportunities for FDA staff. have been greatly enhanced by the availability of seminars, workshops, and conferences. Topics addressed have included modeling in pediatric drug development, nanotechnology, leveraging big data, and tissue phantoms for standardization in photonics. Remote participation in rounds and lectures being held beyond FDA's campus are often available for continuing education credits.

3. Conducting targeted research projects, planned and implemented in close collaboration with FDA scientists - to advance specific regulatory science goals. Projects include furthering understanding of the role of transporters in drug-drug interactions, clarifying current practices around the use of patient prescriber agreements for opioid analgesic drugs, applying machine data classification algorithms to flag events reported in the Vaccine Adverse Event Reporting System and possibly related to autoimmune mechanisms, and developing new imaging methods and standards.

Government Partnerships

FDA partners with other government agencies to facilitate progress in regulatory science in areas of mutual interest to more than one agency.

- The Center for Tobacco Products and NIH have partnered to develop and fund Tobacco Centers of Regulatory Science (TCORS), made up of scientists with a broad range of expertise (e.g., epidemiology, economics, toxicology, addictions, and marketing). The TCORS are expected to demonstrate research excellence and leadership in tobacco regulatory science that will contribute to the science base that FDA will use to develop meaningful product regulation, as it works to reduce the toll of tobacco-related disease, disability, and death in the United States.

- The Sentinel Program, mentioned above, along with other postmarket programs, leverages expertise and data from several federal partners, including DoD, CMS, , AHRQ, SAMHSA, and the VA.

- FDA engages in ongoing regulatory science projects and programs with numerous international regulatory bodies and other groups, including EMA, PMDA, IMI, Health Canada, and PAHO, to provide more efficient use of resources, and increase consistency and predictability in regulatory approaches for data relevant to all regions.

- FDA, in partnership with CDC, USDA, NIH and state public health laboratories, created the GenomeTrakr network, a collaborative effort to use whole genome sequencing for the characterization of foodborne bacteria and as a new molecular epidemiological tool to rapidly investigate outbreaks of foodborne illness.

- FDA, in partnership with CDC and USDA, coordinates the National Antimicrobial Resistance Monitoring System (NARMS), a national public health surveillance system that tracks antibiotic resistance in foodborne bacteria from food animals (USDA), retail meats (FDA), and humans (CDC).

- FDA participates in the Food Emergency Response Network (FERN), an integrated system of local, state, and Federal food testing laboratories to provide early detection of biological, chemical, or radiological threats to the food supply. FDA also participates in the Integrated Consortium of Laboratory Networks (ICLN). FDA contributed to the 2014 ICLN exercise that targeted the emergency response of radioanalytical laboratories during a radiological/nuclear event. This exercise was initiated to assess the ability of FDA's FERN to conduct food safety assessments and post-event food safety surveillance in a nuclear or radiological event that involves alpha and beta radioactivity.

- Interagency Food Safety Analytics Collaboration (IFSAC) - To enhance food safety, three Federal agencies—CDC, FDA, and the Food Safety and Inspection Service (FSIS) of USDA—teamed up in 2011 to create the Interagency Food Safety Analytics Collaboration (IFSAC). The collaboration's goal is to improve coordination of Federal food safety analytic efforts and address cross-cutting priorities for food safety data collection, analysis, and use. Projects and studies aim to identify foods that are important sources of illnesses. IFSAC's activities focus on foodborne illness source attribution, defined as the process of estimating the most common food sources responsible for specific foodborne illnesses.

- FDA collaborates extensively with the Public Health Emergency Medical Countermeasures Enterprise (Enterprise) and DoD partners to foster MCM development and availability. FDA provides subject matter expertise and technical assistance to Enterprise- and DoD-specific committees and working groups that develop MCM requirements, plans, priorities, and policies, and conduct program oversight and integration.

- FDA has an MOU with the Defense Advanced Research Projects Agency (DARPA) to support innovation in medical product development, including for MCMs, and new technologies that can advance regulatory science such as biomimetic models.

- FDA, in partnership with CDC, EPA, USDA, and other Federal agencies deploys with the Federal Radiological Monitoring and Assessment Center (FRMAC). The FRMAC is a Federal asset available on request by the Department of Homeland Security (DHS) and State and local agencies to respond to a nuclear or radiological incident.

- FDA is working with the Federal Communications Commission (FCC) and the Office of the National Coordinator for Health Information Technology (ONC) to develop a health information technology framework.

- FDA is also working with the FCC on wireless technologies and interoperability.

- FDA created the Coordinated Outbreak Response and Evaluation Network (CORE) to manage not just outbreak response, but surveillance and post-response activities related to incidents involving multiple illnesses linked to FDA-regulated human and animal food and cosmetic products.

- FDA partners with NIH and CDC to address issues concerning the public health by applying classical and modern toxicology approaches to study regulated products through the National Toxicology Program. (Recent work at FDA's NCTR on NTP studies includes FDA compounds of interest, such as acrylamide, bisphenol A, and triclosan.)

- FDA created a Veterinary Laboratory Investigation and Response Network (VET-LIRN) to promote human and animal health by collaborating with veterinary diagnostic laboratories to provide scientific information, build laboratory capacity, and train scientists investigating CVM regulated products (animal feeds/animal drugs).

- FDA is a member of the National Interagency Confederation for Biological Research (NICBR), a collaboration of Federal agencies involved in medical research and advanced biotechnology whose goal is to enhance public health, medical research, and biotechnology development by coordinating scientific interactions and leveraging resources.

- FDA is collaborating with the Defense Threat Reduction Agency (DTRA) and the National Center for Biotechnology Information (NCBI) to establish a publicly available reference database that will be critical to developers seeking to validate their candidate multiplex *in vitro* diagnostic tests.

- FDA partnered with NIH to cosponsor a series of scientific workshops on stem cell-derived products to facilitate development of innovative medical products derived from stem cells.

Section C. Demonstrate Regulatory Science Achievements

This section describes examples of accomplishments and activities that illustrate FDA's progress in applying regulatory science to support our regulatory mission. These examples focus on efforts accomplished since the *Mission at Risk Report*, and are organized within the eight priority areas identified in the *Strategic Plan for Regulatory Science*.

1. Modernize Toxicology to Enhance Product Safety

FDA researchers have invested resources in closing gaps in predicting toxicity or safety issues of FDA-regulated products. This work includes the development and use of new computational modeling, in silico, in vitro and in vivo approaches to predict patient responses, the identification of potential biomarkers for monitoring adverse reactions in preclinical species and in humans, and using computational tools to develop data mining tools and build knowledge bases.

The following are examples of these approaches:

- Computational approaches including research in physiologically based pharmacokinetic (PBPK) modeling to improve dosimetry correlations between nonclinical species and individuals who are difficult to study, such as pregnant women and newborns.
- In a collaborative study between the FDA, the Hamner Institute, and others, systems pharmacology modeling approaches were used to evaluate and predict drug hepatotoxicity through development of the DILIsym model.
- Improved and patented methods of in silico modeling were used to build new models to predict drug toxicity to inform population-based safety risks; one such approach might enable precision medicine by identifying patient-specific genetic susceptibilities to individual drugs.
- Novel model systems including zebrafish and human induced pluripotent (iPS) stem cells were used to study developmental toxicity and organ-specific toxicities.
- Bioimaging techniques were developed to allow non-invasive assessment of toxicity. Coupled with cognitive function tests, these techniques were used to demonstrate, in non-human primates, neurotoxic effects of anesthetics that are routinely used in newborns (see example).
- Organ-specific toxicities, such as drug-induced pancreatitis, were examined at the cellular level to improve the predictive usefulness of pre-clinical animal models.
- Genomics, metabolomics, proteomics, and epigenetics were used to identify new biomarkers of toxicity. Work to date includes the identification of potential translational biomarkers of drug-induced liver injury in animals and humans.

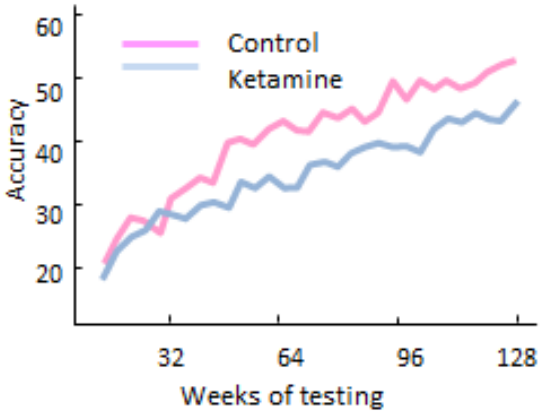
- Next-generation sequencing, bioinformatics, resistomics, transcriptomics, and metagenomics were applied to monitor trends and better understand the mechanism, emergence, persistence, and spread of antibiotic resistance.
- Bioinformatic approaches were used to develop tools (e.g., FDALabel) to assist reviewers and create knowledge bases of divergent information that can be queried to identify previously unknown associations.

Ensuring the Safety of Anesthetics in Children

FDA is leading a program of animal and human research on the safety of anesthetics in young children, and developing noninvasive imaging methods to monitor neurotoxicity of these drugs.

Anesthetics have profound effects on the brain (e.g., deep coma, and suppression of reflex), but these effects are only temporary. Of particular concern to FDA, however, are observations that in the developing brains of newborn mice and rats, anesthetics are highly toxic to nerve cells. Following up on these findings in animals much more similar to humans, FDA researchers exposed rhesus monkeys to the anesthetic ketamine and have followed them for several years. Based on cognitive and behavioral tests highly correlated with measures of human intelligence, they found that there were indeed long-lasting and likely permanent deficits in learning ability in the anesthetized monkeys.

To ensure the safety of patients, especially young children,[1] requiring anesthesia, FDA initiated a public-private partnership in 2010 with the International Anesthesia Research Society (IARS) called SmartTots (Strategies for Mitigating Anesthesia-Related Neurotoxicity in Tots). SmartTots convened meetings of scientific experts to analyze all research in animals and humans related to the safety of anesthetics. They identified three fundamental research questions:



The graph shows how readily rhesus monkeys treated with the anesthetic ketamine as newborns learned a series of increasingly complex cognitive tasks compared with untreated controls. Percent accuracy reflects the number of choices made as the animals learned correct sequences of mechanical manipulations leading to a reward. Learning deficits in exposed animals persisted for years (Paule et al., Neurotoxicology and Teratology 33: 220-230, 2012)

1. What is the spectrum of general anesthetic agents, sedatives, surgical procedures, and/or opiates that cause developmental neurotoxicity? What are the doses, durations, and frequencies of exposure that cause these effects? What are the most vulnerable periods of development?

2. Are there short- and long-term neurocognitive, emotional, behavioral, and/or social outcomes resulting from exposure to anesthetic agents?

3. What approaches can be taken to prevent or mitigate developmental anesthetic neurotoxicity?

SmartTots also supports a competitive granting process to foster research on the effects of anesthetics in children. Notable funded projects include:

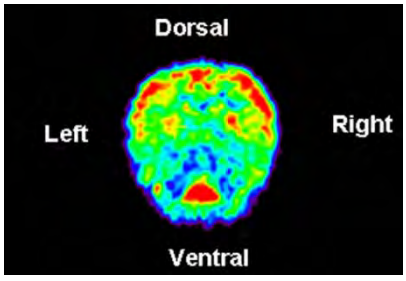
[1] In the United States alone, each year more than 1 million children 4 years of age or younger undergo surgical procedures requiring anesthesia.

The multi-site PANDA (Pediatric Anesthesia and Neuro-Development Assessment) study, which will study the effects early childhood anesthesia before age 3 on long-term neurocognitive function and behavior in healthy children.

Recognition Memory Following Early Childhood Anesthesia, focusing on how the duration of anesthesia exposure and the age of the child affect recognition memory deficits.

Another critical FDA focus has been on developing noninvasive molecular imaging methods to monitor the neurotoxic effects of anesthetics. These methodologies promise to be invaluable in helping to bridge preclinical data with clinical findings and eventually in developing any needed alternatives to current anesthetic treatments. FDA researchers are devising imaging techniques using positive emission tomography combined with specific protein or small molecule probes, to achieve imaging resolution at the cellular level to observe the effects of anesthetics on the developing brain.

As stated in the SmartTots consensus statement in 2012, “millions of young children require surgery and other procedures for serious or life-threatening medical conditions or to improve their quality of life,” and "it would be unethical to withhold sedation and anesthesia when necessary.” Despite the practical difficulties and ethical concerns that make ascertaining toxic effects of anesthetics directly in children extremely difficult, animal studies under controlled, reproducible conditions can help us find ways to ameliorate risk. By building inclusive research partnerships with professional societies, the academic community, advocacy groups, industry and organizations, and conducting a program of cutting edge research at NCTR, FDA is ensuring that we will be prepared to meet this complex regulatory challenge.



Contamination of Pet Food and Baby Milk Formula with Melamine and Derivatives

FDA collaborated with other Federal agencies to develop rapid, precise methodologies that enabled development of novel histopathologic and analytical approaches for evaluating melamine and related toxins in food.

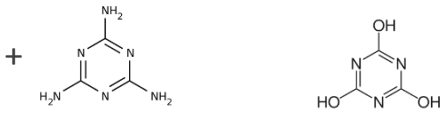
In 2007, adulterated imported pet food ingredients caused fatal kidney disease in thousands of cats and dogs in the United States. This adulteration led to a wide-scale voluntary recall of pet food. Investigations revealed that “scrap melamine” containing cyanuric acid had been incorporated in wheat flour to simulate higher protein content. In 2008 in China, melamine added to baby formula led to the hospitalization of approximately 300,000 children with kidney disease and the death of at least 6 infants.

FDA regulatory scientists respond to the challenge of melamine adulteration

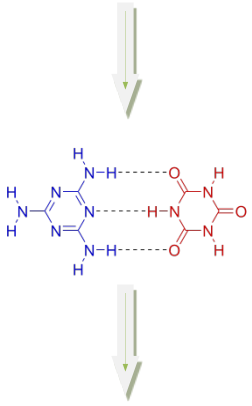
These adulteration events raised worldwide concern about the presence of melamine and derivatives, including cyanuric acid, in food products. Although previous toxicology studies indicated that melamine and cyanuric acid administered alone presented very low toxicity, it was determined that co-exposure to these compounds can result in the formation of tiny crystals of melamine cyanurate in the kidneys which obstruct renal tubules, leading to kidney failure and death.

These new observations posed a significant regulatory challenge for FDA, due to the urgency of the response required and the scarcity of information on methods for quantifying melamine and cyanuric acid in food products and on the toxicities of these compounds when they are combined. FDA scientists collaborated across product centers and offices to develop an integrated response.

Analysis of melamine and derivatives in food products. To enable the analysis of melamine and derivatives in pet food products and milk-containing products, FDA developed and validated analytical methodologies based on the use of advanced sample preparation and mass spectrometry and devised analytical standards that were thereafter followed by the industry and a number of other regulatory agencies.



Melamine **Cyanuric acid**



Melamine cyanurate

Tubular Obstruction

Kidney Failure

Toxicological evaluation of the combination of melamine and cyanuric acid. In a multicenter effort, FDA conducted toxicological studies (some of them under an interagency agreement between FDA and the National Toxicology Program of the National Institute of Environmental Health Sciences). Key outcomes were the following:

- A new, simple, but highly sensitive histopathologic procedure based on the wet-mount of animal kidney tissue samples enabled more sensitive detection of melamine cyanurate formation.
- Fast-track studies in a fish model provided definitive evidence that the formation of crystals was the result of combined exposure to melamine and cyanuric acid and laid the foundation for subsequent mammalian studies.
- In a range of exposure scenarios, the toxicokinetic profiles of melamine, cyanuric acid, melamine and cyanuric acid in combination, and melamine cyanurate were determined in an animal model using a novel, highly sensitive method (based on ultra-performance liquid chromatography-tandem mass spectrometry).
- It was demonstrated in animal models that several urinary proteins may serve as noninvasive biomarkers for the detection and monitoring of melamine and cyanuric acid-induced kidney damage.
- Genes whose expression is modulated by melamine and cyanuric acid-induced kidney damage and which may constitute sensitive endpoints of toxicity were identified.
- Mammalian dose-response studies showed that melamine and cyanuric acid in combination is substantially more toxic than either compound alone.

Overall, these studies reflect a coordinated research effort between FDA centers and laboratories, where a combination of expertise enabled an in-depth evaluation of the toxicological profile of a combined exposure to melamine and cyanuric acid. These studies relied not only on traditional approaches to toxicology, but also on the development of novel histopathological and analytical approaches, including advanced mass spectral methodologies, and the use of proteomic, metabolomic, and genomic techniques. Novel endpoints and biomarkers of toxicity that can be the foundation of future studies at FDA were discovered.

2. Stimulate Innovation in Clinical Evaluations and Precision Medicine to Improve Product Development and Patient Outcomes

Evaluating the safety and effectiveness of medical products remains one of the most challenging steps in the translation of new scientific discoveries into viable medical treatments. Working with the clinical trial community, patient organizations, and other stakeholders, FDA has made significant contributions to advancing the science of clinical trials on several fronts.

Clinical trial designs that incorporate adaptive designs and enrichment strategies are being used to generate data that identify which patients benefit from an experimental therapy. Trials suited for the device development arena are incorporating Bayesian designs and using non-randomized controlled trials to do the same. New bioequivalence methods and clinical study requirements for determining biosimilarity are being developed. FDA statisticians have contributed to the design of efficient master protocols for cancer and antimicrobial therapies. These protocols incorporate biomarker information and reduce the number of patients required. Additional new tools that aid in the design and analysis of clinical trials include pharmacometric models to optimize dosing strategies, disease models that inform the design of trials, models that inform bioequivalence determinations, and models that predict device performance.

New biomarkers and clinical outcome assessments have been developed and integrated into the regulatory process by formal qualification processes for drugs and devices. FDA has enhanced infrastructure for receipt, storage, and analysis of digital applications by specifying data standards for preclinical and clinical studies, building digital preclinical and clinical trial repositories, and developing data mining and analysis tools to make the review process more efficient and effective.

FDA's significant advances in facilitating the realization of precision medicine are detailed in a recent report Paving the Way for Personalized Medicine: FDA's Role in a New Era of Medical Product Development. Advances include a focus on pharmacogenomics, personalized devices, and clinical trial designs focused on defined subgroups.

Some recent examples of FDA advances in clinical evaluation strategies and precision medicine include:

- Developed, in a collaboration with Friends of Cancer Research, a master multi-drug, multi-arm protocol for lung cancer. The protocol will involve large-scale screening through which patients are assigned to treatment based on biomarker status.
- Incorporating improvements in device trials as one of three major areas of focus for the Medical Device Innovation Consortium.
- Qualifying an electronically-administered patient-reported outcome (PRO) to measure symptoms of acute bacterial exacerbation of chronic bronchitis in patients with chronic obstructive pulmonary disease.

- Creating a clinical trials repository and integrated data mining and analysis tools to facilitate regulatory analysis and research
- Developing disease progression models for Parkinson's disease to inform design of trials to discern disease modifying effects
- Validating earlier sustained virologic response clinical end points for regulatory approval and dose selection of hepatitis C therapies.

Evaluating a Surrogate Endpoint That Could Speed Development of New Cancer Therapies

FDA has explored surrogate endpoints designed to accelerate clinical evaluation of new cancer drugs.

A fundamental obstacle to drug development for many chronic diseases is the time needed to measure clinical benefit (for example, in terms of what is often considered the gold standard, overall survival). FDA has regulatory mechanisms[1] in place that can allow for accelerated drug approval based on the drug's effect on a surrogate endpoint, i.e., a laboratory measurement, radiographic image, physical sign or other outcome that can predict, but is not itself a measure of, real benefit.

Receiving such approval requires sponsors to conduct what are called phase 4 confirmatory trials to show that patients ultimately benefit in terms of overall survival or some other clinically meaningful measure. We describe FDA's recent research to assess the validity of one surrogate endpoint in the context of trials of neoadjuvant (before surgery) treatments for women with breast cancer.

Pathologic complete response as a surrogate endpoint in breast cancer trials

Following neadjuvant therapy[2], a pathology finding of no detectable cancer in the breast and in some cases in the axillary nodes is known as pathologic complete response (pCR). pCR is often used as an endpoint in clinical trials assessing the effectiveness of different therapies. In 2012, FDA published guidance on the use of this endpoint, including a recommended common definition, and the design of the trial that should be used to address a breast cancer drug's efficacy in the preoperative setting. That same year, FDA granted accelerated approval to Perjeta (pertuzumab) for certain patients with HER-2-positive breast cancer,[3] based on an increased frequency of pCR. This decision was supported by previous evidence of pertuzumab's efficacy in the treatment of advanced or late-stage (metastatic) HER2-positive breast cancer.

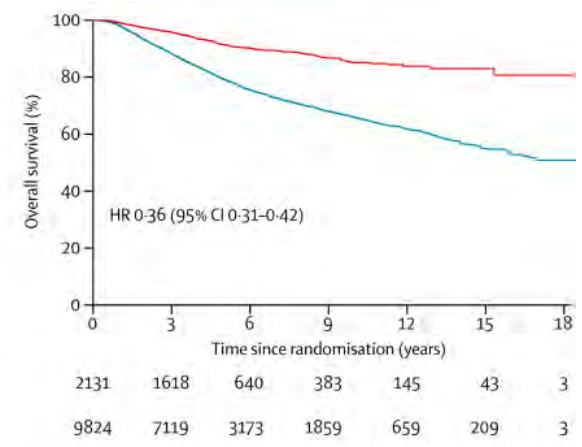
FDA's investigation of the usefulness of pCR

FDA researchers sought to develop a more definitive understanding of the suitability of pCR as a surrogate for real clinical benefit in trials of neoadjuvant treatments for breast cancer. In a meta-analysis of 12 clinical trials (nearly 12,000 patients) of neoadjuvant chemotherapy for breast cancer, they measured the strength of the association between pCR and overall survival and event-free survival in patient groups defined by cancer type and treatment.

[1] These are *Priority Review* and *Fast Track*

[2] Chemotherapy, targeted therapy or hormone therapy given before surgery for breast cancer.

[3] Breast cancer that tests positive for the protein human epidermal growth factor receptor 2, tends to be more aggressive, and can be effectively treated with Trastuzumab.



The plot shows the number of patients surviving at a given time after entering the clinical trials studied in FDA's meta-analysis. Patients who achieved pCR (red line) had a clear survival advantage over those who did not (blue line). Statistical analysis did not confirm an association between a treatment's effect on pCR and its effect on survival. Possible explanations are the fact that in the available studies (typically comparing one or more treatments) there were not strong treatment-specific differences in terms of pCR frequency and the fact that the kinds of breast cancer studied were highly heterogenous.

Among their key findings were the following:

- At the level of individual patients, there was a strong association of pCR and event-free and overall survival.
- The strength of the patient-level association between pCR and survival was sensitive to the definition used for pCR.
- The association between pCR and long-term survival was highly dependent on the breast cancer type as defined by the presence or absence of hormone receptors, expression of HER-2, and tumor grade.
- The association of pCR with event-free survival tended to be stronger in patients treated with trastuzumab.

Despite the strong association between event-free survival and pCR at the level of the individual patient, the analysis did not confirm an association between a treatment's effect on the frequency of pCR and its effect on survival. This may have been because the available studies, which by necessity compared alternative treatments, were not ones in which strong treatment differences were observed. Also, the kinds of breast cancer studied were highly heterogeneous. However, the strength of the association of PCR with long-term outcome in individual patients provided justification for further consideration of this endpoint in an accelerated approval process. And the research had implications for the design of future trials that could validate use of this surrogate endpoint. Relatively large differences in the frequency of pCR in compared trial arms may now be attainable with newer targeted therapies, and FDA's research suggests that it may be necessary to examine trials in which cancers are similar according to stage and molecular markers.

Using Bayesian Statistics to Evaluate the Safety and Effectiveness of Medical Devices

Clinical trials to evaluate the safety and effectiveness of medical devices have traditionally been "closed systems." That is, once the parameters of the study (e.g., duration, number of patients) are established, little or no deviation from the plan is permitted.

> FDA regulators encouraged sponsors to use a dynamic statistical strategy that can dramatically reduce the time it takes clinical trials to generate data the agency needs to evaluate the safety and effectiveness of new devices.

Moreover, traditional clinical trials do not statistically analyze evidence of the safety and effectiveness of similar devices. Even when new evidence on safety and effectiveness is discovered during the course of the trial (which can take several years), the trial usually must continue unmodified in order to be considered valid.

Traditional clinical trials also don't permit the protocol to be amended (e.g., duration and number of patients required to demonstrate safety and effectiveness) even if initial findings might support such changes.

Therefore, to make such trials more flexible while maintaining scientific rigor, FDA encourages medical device manufacturers to use Bayesian statistics in designing their trials.

Derived from the 18th century theorem of Thomas Bayes and refined in the late 20th century, Bayesian statistics permit investigators to incorporate prior, new, or evolving evidence during the course of the trial; i.e., to learn from evidence as it accumulates, and, based on interim analyses, to make appropriate changes in the trial protocol. Thus, the trial designer can combine new and existing information about similar devices and the medical condition being treated with analyses conducted during the course of the ongoing study, as well as with new information from other studies. This enables the study to unfold dynamically, as part of a continual data stream in which newly available knowledge is incorporated into the trial. Specifically, Bayesian statistics allows investigators to adjust study parameters to reflect the study's interim results, data from clinical trials conducted overseas, from the manufacturer's own previous studies, and from patient registries. Mid-stream changes could include decreasing or increasing the number of subjects or the time required to demonstrate safety and effectiveness. Bayesian statistics can also facilitate a decision to stop a trial early, either because completion would be futile, or because interim data predicts success.

This enables safe and effective new devices to reach patients more quickly.

By 2011, FDA had approved at least 17 medical devices that were evaluated through clinical studies using Bayesian statistics. In particular, orthopedic devices indicated for treatment of cervical and lumbar degenerative disc disease causing pain and functional problems are particularly suited to this approach.

For example, Bayesian statistics enabled statisticians to design an adaptive trial that used a mathematical model to predict patient results at the 24-month follow-up based on previous visits at 3, 6, and 12 months. This strategy shortened considerably the time FDA needed for approval of two cervical disc products.

3. Support New Approaches to Improve Product Manufacturing and Quality

FDA has made concerted efforts to understand how new science and technology could be applied to increase the efficiency, accuracy, and manufacturing quality of FDA-regulated products. The safety and effectiveness of FDA-regulated products may depend on a number of factors, including design, manufacture, quality assurance, packaging, labeling, storage, installation, and servicing. Research in these areas focuses on improving the initial product design and manufacturing processes as well as techniques to detect problems when they arise.

The following examples illustrate the range of FDA's accomplishments and ongoing activities in this area of regulatory science:

- Investigated the ability of next-generation sequencing (NGS) data to evaluate product purity and quality. For example, NGS data has been used to determine the consistency of live virus vaccines and to screen vaccine cell substrates and other vaccine manufacturing intermediates for contamination with infectious agents.
- Developed and evaluated methods to use high-resolution NMR, mass spectrometry, aptamers and other high resolution analytic methods to identify structural determinants of recombinant therapeutic proteins to prepare for evaluation of biosimilars.
- Developed and evaluated novel analytic methods to assess product purity and identity of nanotechnology-based regulated products.
- Developed laboratory analytical and field examination procedures addressing various attributes of higher risk medical devices and radiation-emitting products.
- Used NGS data to detect and track the source of foodborne outbreaks and human pathogens with antimicrobial resistance markers in food animals and animal feed.
- Developed and implemented hand-held monitors based on Raman spectrometry to screen imported FDA-regulated products for evidence of contamination or to identify counterfeit products.
- Determined root-cause failures of device safety issues in devices such as Huber needles, ventilators, and infusion pumps.
- Developed standards to prevent misconnection of different sets of small-bore connectors used for IV, feeding, tracheotomy, and discharge tubes to prevent contamination and serious adverse events.

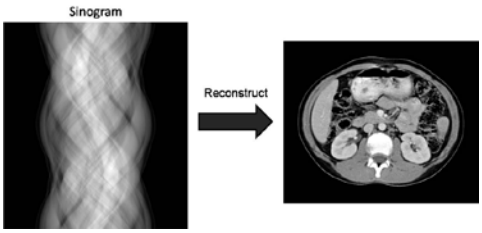
Measuring Image Quality to Help Reduce Radiation Exposure from CT Exams

FDA has developed methodologies for assessing the quality of reconstructed CT images so that radiation exposure can be reduced.

The increasing use of computed tomography (CT) has created concern about patient radiation exposure and the associated impact on public health. To address this issue, CT manufacturers are making efforts to implement new technology that can allow patient imaging at a lower radiation dose without loss of image quality.

A CT device includes software that "reconstructs" raw X-ray data (Figure 1a) into a recognizable image of human anatomy (Figure 1b). Recently, CT manufacturers began implementing a type of reconstruction called iterative reconstruction (IR).

Figure 1a **Figure 1b**



IR algorithms may potentially achieve the same level of image quality as older algorithms, using less radiation. However, the increased sophistication of these algorithms poses unique challenges to regulators. In particular, measuring the amount by which a given IR algorithm can reduce dose without compromising image quality requires an assessment of image quality. The traditional metrics of image quality include image noise and resolution; however, IR algorithms generate images for which the noise and resolution vary across a single image.

Standardized methods for measuring dose reduction would help CT buyers, CT vendors, and medical physicists and would also be useful to FDA, which regulates device labeling.

Task-Based Assessment

The best way to measure dose reduction by IR is a "task-based" assessment of CT images: assessing image quality as the ability of a reader to perform a given task (like finding a lesion) on the image. The task should simulate what a radiologist would perform in actual clinical practice, e.g., finding lung nodules in an image of the lung. A task-based assessment should allow determination of uncertainties, require a practical number of images, and be readily standardized. For standardizability, the images are generally of "phantoms" designed to test CT devices, rather than humans. FDA and industry, working together, have developed custom phantoms for the assessment of IR images. In a task-based study, the image reader, or "observer," can be a "model observer"— a computer program whose performance on simple tasks replicates human performance. Because model observers are inexpensive, fast, and yield consistent and reproducible results, FDA has encouraged manufacturers to use them in validation studies.

Task-based assessments (Figure 2) have streamlined the clearance process for IR algorithms, saving industry time and money.

Figure 2

Task-based studies involving phantoms are simplistic compared to actual clinical scenarios, and FDA has recommended that manufacturers attach appropriate disclaimers to IR algorithm labeling. FDA also encouraged manufacturers to make public information about how they measured dose reduction in their device, so that their measurements can be independently repeated.

Nonclinical testing is only part of the information that FDA reviews during clearance of an IR algorithm. FDA also evaluates descriptive information and, when necessary, clinical data.

FDA Collaborates with Industry

Working with industry, FDA has developed methods to measure dose reduction by IR algorithms. FDA has published two journal articles[1,2] on these methods. In addition, FDA is developing open-source software to further streamline the regulatory process.

Since the FDA–industry effort began, four CT vendors have obtained clearances for IR algorithms. Three of these algorithms were cleared with labeling identifying the specific amounts by which they could reduce radiation dose.

Identifying the Cause of Thrombosis Linked to Immunoglobulin Treatments

FDA studies led to the development of assay protocols to evaluate IGIV products for thrombogenicity.

Immune globulin intravenous (IGIV) is a blood-derived product containing pooled immunoglobulin (antibody) fractions extracted from the plasma of over 1000 donors. Licensed indications include immune deficiencies and autoimmune disorders.

Adverse events triggered investigation

Although generally considered safe, IGIV products occasionally cause mild to moderate adverse events, such as low-grade fever, headache, malaise, and nausea. One less common, but serious and potentially fatal complication, is the occurrence of thrombotic events (TE), which are likely to develop within 24 hours of IGIV administration. They include myocardial infarction, stroke, deep venous thrombosis, and pulmonary embolism.

In light of these rare, serious adverse events, precautionary labeling for IGIV products has been recommended since October 2003; however, the causes of IGIV-mediated thrombosis remained uncertain and have been generally attributed to the patient's condition, since many patients are already considered at risk for thrombosis.

Despite reports of TE events over the years, lot-associated clusters were uncommon for this product. Then in May 2010, AEs linked to two lots from one manufacturer (stroke and myocardial infarction in several patients) prompted the company to put a hold on the release of these lots. After a subsequent investigation failed to find lot abnormalities, the company provided four blinded lots to FDA for lot testing at the agency's request: Lot A (2 strokes), Lot B (control), Lot C (non-thrombotic AEs), and Lot D (2 myocardial infarctions during infusion). The manufacturer also sent a second set of blinded lots to enable FDA researchers to confirm the results.

CBER optimized assay to study products

In July of 2010, using an existing thrombin generation assay that FDA's laboratory of hemostasis adapted and optimized for testing blood-derived products, FDA scientists recorded the time course of coagulation enzyme thrombin activity during coagulation of human blood plasma. Lots A and D, which had been implicated in thrombotic events, induced faster and higher thrombin generation than control lots. The researchers confirmed these results by recording blood clot formation in a small microchamber under a specially designed video microscope. Lots A and D again demonstrated higher rates of clotting than control samples B and C.

The researchers continued their investigation using the quantitative, high-throughput thrombin generation assay that generated the initial FDA findings. They compared the implicated lots A and D

[1] J.Y. Vaishnav et al., Medical Physics (2014)

[2] L.M. Popescu et al, Medical Physics 40, 11908 (2013)

to other random lots of 5 marketed products. (Since then [August 2010], additional IG products with procoagulant activity were identified by FDA and others.) The procoagulant activity of the implicated lots was significantly higher than other products or even other lots of the same product, suggesting that the thrombin generation test can be used for identification of potentially thrombogenic lots.

In early August 2010, FDA shared our data with the company, which confirmed the results and proactively established product evaluation methods using similar coagulation assays. On August 20, the company voluntarily withdrew 31 lots from the U.S. market. Subsequently, many more international reports of thrombotic events were received, possibly stimulated by the initial reports. By the end of September, all product lots were voluntarily removed from the U.S. market.

Factor XIa identified as product impurity

Further FDA studies focused on identifying procoagulant impurities and developing lot release testing assays to evaluate other products. FDA's laboratory used a panel of plasma-derived and synthetic coagulation inhibitors to identify coagulation factor XIa and exclude factors XIIa and kallikrein, both of which were previously suspected as thrombosis-causing impurities in IG products.

They then used purified Factor XIa to demonstrate similar dose-dependent reactions with implicated lots, which suggested that Factor XIa is the procoagulant impurity in implicated lots. This finding enabled them to develop a Factor XIa-calibrated bio-assay for thrombogenic impurities.

To facilitate harmonization of IG thrombogenicity testing, an interim international standard of Factor XIa activity was developed by WHO in 2012 (in collaboration with FDA). In 2014 it was replaced by WHO's first international biological standard. The suitability of these standards is being evaluated in the ongoing collaborative multinational laboratory investigation of thrombogenic IG samples provided by several manufacturers.

The assay protocols developed by FDA have since been shared with the industry and regulators across the world. This work also contributed to the ongoing development of a lot release assay currently under development by FDA.

4. Ensure FDA's Readiness to Evaluate Innovative Emerging Technologies

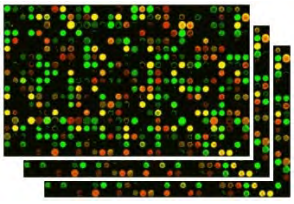
FDA has invested heavily in regulatory science to support readiness to evaluate emerging technologies. To ensure readiness, FDA needs to recruit the scientific expertise needed to address new areas as well as provide resources to train/retrain existing staff to provide up-to-date knowledge of new technologies. By performing its own research on emerging technologies, FDA can identify and fill the knowledge gaps necessary to support regulatory decision-making.

The following examples illustrate the range of accomplishments and ongoing activities in this area of regulatory science:

- Evaluated and used 3-D printers to understand the limits and capabilities of this new technology in developing regulated products
- Developed Fatigue Test Methods for Medical Devices composed of bioresorbable polymers Including Peripheral and Coronary Stents, Bone Screws and Related Components
- Developed analytical and field test protocols for Automated Non-Invasive Blood Pressure Monitors (Sphygmomanometers) for Imported Devices Labeled for Home and Public Use
- Created a General Testing Protocol and Test Methods for Automated External Defibrillators (AEDs)
- Developed Methods to Evaluate and Characterize New Test Equipment for Suitability in X-ray Compliance Testing
- Created new approaches to identify and understand critical product quality attributes of complex products, such as stem cell-derived products (both animal and human) and complex systems of medical devices
- Developed methods and models to assess the toxic effects of FDA-regulated products containing engineered nanomaterials
- Evaluated the health impact of probiotic nutritional supplementation in mice
- Developed analytic methods and preclinical models for assessment of hemoglobin-based oxygen substitutes
- Established genomic sequencing reference material and constructed a library of definitive sequences for common pathogens to serve as a foundational body of data that could be used in the creation of future diagnostic tools, devices, and therapies

Realizing the Promise of Precision Medicine Through Quality Control

FDA consortia evaluated the validity of microarray predictive outcome models and the potential of a more comprehensive unbiased quantification of RNA sequencing.



The 2007 Mission at Risk Report predicted that "integration of individual genomic information with technological advances in quantitative, unbiased and hypothesis-driven biomarkers of drug action is likely to hasten the progressive personalization of medicine." FDA had just completed the first phase of the MicroArray Quality Consortium (MAQC) to meet challenges posed by data in regulatory submissions from microarray platforms used to simultaneously measure expression of large sets of genes. MAQC-I established that microarrays could reliably identify differentially expressed genes across sample classes or populations and that high intra-platform reproducibility across test sites was feasible.[1]

MAQC-II

The value for drug development (and medicine in general) of the data collected using microarrays is that they can be used to develop predictive (or discriminative) models. For example, comprehensive information on gene expression in a group of cancer patients treated with a given drug might allow for the identification of a profile of gene expression (molecular signature) that would predict which patients would be likely to respond to treatment or not. For example, MammaPrint is an FDA-approved diagnostic test that uses microarray technology to assess the risk that a breast tumor will metastasize to other parts of the body and to guide treatment.

Despite their promise, the scientific community has found the development of these models challenging. In response, FDA initiated MAQC-II, a joint effort of 97 organizations and over 200 investigators to identify critical factors for success. Thirty-six separate teams generated thousands of models that were, in effect, a comprehensive sampling of the approaches in current use. Then, the validity of the models was independently evaluated using external data. The main findings were the following:

- Performance of models developed from gene expression data was highly dependent on the disease and toxicity endpoints being predicted.[2]
- The choice of mathematic and statistical approaches had minimum impact on the results.
- Multiple models of comparable performance can be developed for a given endpoint.
- The success of different teams varied significantly, suggesting that expertise and modeling experience are important factors.

Subsequent work from MAQC-II also suggested that the predictive value of molecular signatures was often robust across different platforms. Based on its findings, MAQC developed modeling recommendations for the benefit of the scientific community.[3]

[1] This first phase of MAQC culminated with the publication the FDA guidance to industry *Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling* and over numerous publications in peer-reviewed journals.

[2] Among the endpoints studied, disease progression endpoints were difficult to predict.

[3] The MAQC Consortium, The MicroArray Quality control (MAQc)-ii study of common practices for the development and validation of microarray-based predictive models. *Nature Biotech* 28, 827–838.

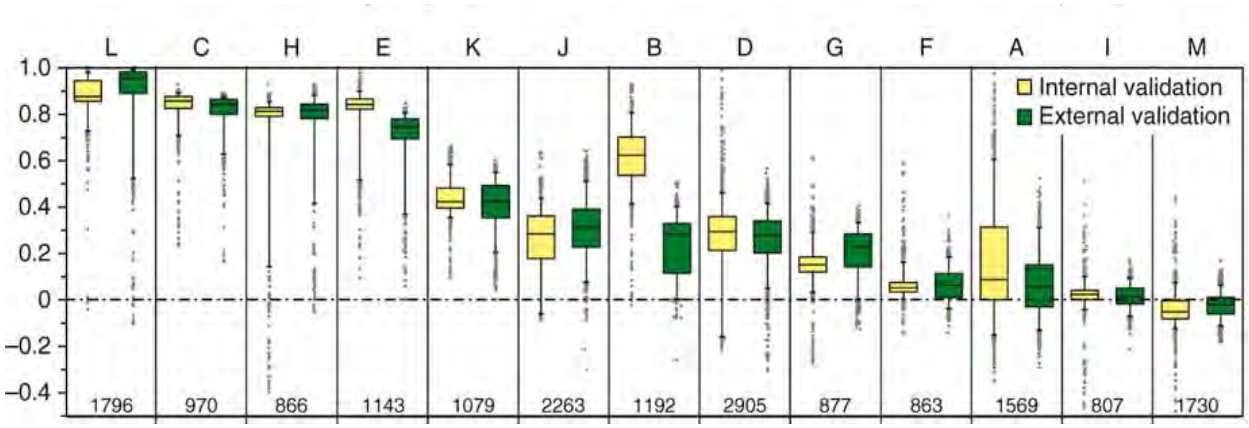
MAQC-III

Recent developments in next-generation sequencing (NGS) allow investigators a much more comprehensive view of the full diversity of gene expression, including RNAs not expressed as proteins and rare genetic variants, and alternative gene transcripts.

In MAQC-III, also known as Sequencing Quality Control (SEQC), 180 investigators from 73 organizations are focusing on the potential of RNA-Seq, an approach based on NGS that can allow a more comprehensive unbiased quantification of the RNAs in a sample. Key topics under investigation include:

- Performance of RNA-Seq in terms of accuracy, and cross-laboratory and cross-platform reproducibility
- Comparison of RNA-Seq with microarray technology
- The effect of different bioinformatics approaches on result
- The usefulness of RNA-Seq in generating biomarkers

- The potential of RNA-Seq to advance toxicogenomics.



The success of the models contributed to MAQC-II was highly dependent on what was being predicted. The plot shows how the 18,000 models developed by 36 teams performed when tested against data the consortium sent to the modeling teams (internal validation, yellow) or against data not provided to the teams (external validation, green), with 1.0 on the vertical axis representing perfect performance and zero representing no predictive value. For some events (e.g., whether a rat had been given a toxic drug (C), or whether a breast cancer patient's tumor tested positive for the estrogen receptor (E), models tended to be very successful); for other kinds of events or outcomes, model development was much less successful (e.g., predicting which breast cancer patients would respond to chemotherapy (D) or predicting survival in multiple myeloma patients (G). As a positive control, the modelers were given data according to sex of the patient (H and L) and as a negative control random data were provided (I and M). (From the MAQC Consortium, 2010, Nature Biotechnology 28, 827–838.)

Rapid Screening of Pharmaceutical Materials Using Portable Spectrometers

FDA screening technologies enable rapid, accurate testing at mail and import facilities for pharmaceutical and herbal dietary supplement adulterations

In cooperation with ORA, the portable instruments have been used since 2014 to screen active pharmaceutical ingredients classified as domestic imports for the presence of economically motivated adulteration (EMA); they are also being used to screen dietary supplements and herbal remedies for the presence of undeclared pharmaceutical ingredients.

FDA has built, developed, piloted, and supported a rapid screening program that conducts surveillance of pharmaceutical materials at domestic and foreign sites. The primary aim of the program is to increase the number of pharmaceutical materials that undergo physical testing. The program has been in place domestically at mail and import facilities since 2010; rapid screening instruments were sent to Mexico City and India FDA international offices in 2013.

Portable Raman and Near Infrared Methods

Raman and near infrared (NIR) are complementary spectroscopic techniques used to acquire the unique molecular fingerprints of different substances. This enables these techniques to differentiate between chemicals that appear identical to the unaided eye. One of the greatest advantages of these techniques is their ability to rapidly interrogate the sample under study in its original packaging without additional sample preparation that might destroy the sample.[4]

The DPA rapid screening program uses the Raman and near infrared instruments to conduct surveillance of pharmaceutical materials vulnerable to EMA. Screening for EMA is primarily done on raw materials—APIs and excipients.

The initial project undertaken by DPA using Raman and NIR screening of EMA-related systems focused on 26 batches of imported glycerin, a common excipient, for adulteration by diethylene glycol (DEG). The screening methods had a limit of detection for DEG in glycerin of 0.32%. No DEG was detected in any of the batches tested. Of the 26 total batches screened, nine samples were sent to the lab for confirmatory testing by compendial methods.

For the month of July 2012, 15% of large glycerin shipments were physically tested with the Raman methods, a much larger percentage than would have been possible if traditional laboratory testing was used. None were found to contain adulterants.

Training of FDA investigators is currently underway to support screening of active pharmaceutical ingredients using spectral library methods, which are able to screen more than 50 different materials at risk for EMA.

[4] Rodriguez, J. D.; Gryniewicz-Ruzicka, C.M.; Kauffman, J. F.; Arzhantsev, S.; Saettele, A.L.; Berry, K.A.; Westenberger, B.J.; Buhse, L.F. Transferring Raman Spectral Libraries and Chemometric Based Methods Between Different Instruments and Platforms. *Am. Pharm. Review* **2013**, 16, 9-18.

Portable Ion Mobility Spectrometry (IMS) Methods

IMS is a high-throughput separation method used to detect and identify volatile and semi volatile organic compounds, based on the time it takes for the ionized species to travel through a drift tube. This capability has made IMS popular for a variety of uses, including detecting undeclared prescription pharmaceutical products and other potentially harmful chemicals often found in herbal dietary supplements claiming to enhance weight loss.

Sibutramine, which was removed from the marketplace due to adverse events, is one of the most common undeclared pharmaceuticals found in weight loss products.[5] The DPA rapid screening program developed an IMS method to screen weight loss products for the presence of undeclared sibutramine and two of its analogues. Six portable IMS instruments are currently deployed at

international mail facilities in the United States to screen weight loss products for undeclared sibutramine and its analogues.

In a recent field investigation, FDA used portable IMS instruments to analyze 225 weight loss products.[6] Forty-two of these products triggered an alarm on the IMS instrument and were sent to the laboratory for confirmatory analysis. Twenty-three control samples that resulted in a "Pass" analysis were also collected and sent to the laboratory for additional analysis. All 42 samples failing IMS field screening were confirmed by the laboratory to contain sibutramine, and five of these contained other undeclared pharmaceuticals. The 23 additional samples were found to contain no sibutramine, confirming the determination that was made in the field study. The 42 sibutramine-containing weight loss products were destroyed, thus protecting U.S. consumers from herbal products containing undeclared drugs. Due to the success of the IMS screening method for sibutramine, additional alarms have been added to the portable instruments for other pharmaceuticals commonly used in weight loss products and FDA began deploying these devices in 2014.

[5] Kauffman, J.F.; Rodriguez, J.D.; Gryniewicz-Ruzicka, C.M.; Arzhantsev, S.; D'Sa, A.; Uratani, B.; Wolfgang, S.; Westenberger, B.J.; Buhse, L.F.; Dunn, J.D.; Mecker-Pogue, L.C. Securing the supply chain through Rapid Screening of pharmaceutical materials. *BioPharma Asia*. **2013**, 3, 28-37.

[6] Rodriguez, J. D.; Gryniewicz-Ruzicka CM; Arzhantsev S; Kauffman, J.F.; Buhse, L.F. Rapid Screening Methods for Pharmaceutical Surveillance. In Science and Law: Analytical Data in Support of Regulation in Health, Food, and the Environment. Eds. William Town, W. and Currano, J. **2014**, In Review.

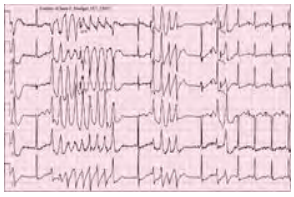
5. Harness Diverse Data through Information Sciences to Improve Health Outcomes

In the last several years, FDA scientists have greatly expanded the development and use of new methods and tools for data mining, modeling, simulation, data visualization, active surveillance and risk assessment, applying them in a variety of regulatory contexts. FDA has worked actively to expand access to a broad range of new external data sources while improving capabilities for mining in-house data for knowledge building, analysis, modeling, and simulation. New methods and tools for the analyses of large datasets have been applied to understanding clinical endpoints, dose estimation in special populations, safety assessment and prediction, and product performance. Some efforts are exploratory, some are providing practical, auditable tools to aid reviewers, and others are being used to inform regulatory decisions. The following examples illustrate FDA's range of accomplishments in this area of regulatory science:

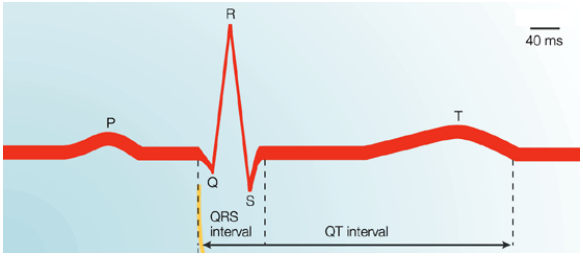
- Used the Mini-Sentinel pilot program to leverage electronic health care records from over 150 million patients across 18 data partners to support hundreds of queries related to post-marketing surveillance of the safety of medical products
- Developed a computational *Virtual Family* of anatomically correct models to investigate how various devices interact with the body
- Implemented natural language text mining tools to interrogate FDA drug product labels, MEDLINE abstracts, and gene/protein databases to find causal interactions between drug pharmacology and unexpected clinical adverse events
- Developed and applied risk-based models to guide selection of facility and clinical trial sites for inspection
- Explored the potential for mining social media and other web sources to detect adverse event and safety signals
- Applied data mining and natural language processing of free text to multiple information sources to refine post-market surveillance
- Expanded the available quantitative structure-activity models to predict toxicity
- Developed models to bridge existing clinical data to guide dosing recommendations in pediatric populations
- Launched the CERES (Chemical Evaluation and Risk Estimation System) database to enhance chemical evaluation and risk estimation for pre- and post-market review of food ingredients (The system enables FDA to fully leverage available data through modern computational and predictive methods for pre-market review and post-market monitoring of food ingredients and packaging materials.)

Improving Evaluation of Cardiac Safety During Drug Development: the ECG Warehouse

FDA spearheaded development of a large patient ECG repository to support efforts at identifying the potential of new drugs to cause dangerous heart arrhythmias.



Over the last several decades, a diverse set of non-cardiac drugs were shown to cause a change in the electrical activity of the heart that manifests itself as a prolongation of the QT interval on an electrocardiogram (ECG). QT prolongation is associated with a heart arrhythmia, torsade de pointes, which can result in uncoordinated contraction of the heart's ventricles (ventricular fibrillation), a sometimes fatal event. In response to an unfolding crisis, FDA and its counterparts in Europe and Canada developed guidelines for the testing of most new systemic drugs in terms of their effects on the QT interval. The required *thorough QT* (TQT) *study*, an examination of a drug's effects in health individuals in the early clinical phase of drug development, is intended support a conclusion that a new drug, at the maximum tolerable dose, does not prolong the QT interval to a clinically significant extent.[1]



A typical ECG tracing of a single heartbeat. The QT interval is shown. Because many drugs have been shown to cause a prolongation of the QT interval, that is associated with a potentially fatal irregularity in heart function called torsade de pointes, drug developers are required to conduct a thorough QT study early in clinical development to rule out, with high confidence, a lengthening of the QT interval of about 10 ms. The bar at right corresponds to 40 ms.

The TQT study and its regulatory review is a complex undertaking for many reasons. The QT interval as recorded by the ECG changes throughout the day and according to heart rate. Placebo arms and positive control arms and precise establishment of a baseline QT interval are required. Because very small increases in the QT interval appear to be associated with risk, studies that assess QT effects require collection of many thousands of ECGs. Regulatory review of TQT studies has engaged the expertise of statisticians, cardiologists, pharmacologists, and experts in modeling and simulations, and raised a number of complex scientific issues that are topics of current research.

The ECG Warehouse

A central element of FDA's efforts in response to the regulatory challenge posed by drug-induced torsade de pointes was the development in conjunction with Mortara Instruments of an ECG repository that now contains more than 6 million anonymized tracings from TQT studies and related studies in a standard digital format along with key descriptive data, such as age, gender, and drug treatment group. Since the Mission at Risk report, topics of research based on this unique resource include the following:

- Determining a more accurate approach to adjusting for circadian variation in TQT studies

[1] The TQT study was described in the International Conference on Harmonization E14 document *The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-arrhythmic drugs.*

- Leveraging the relationship between *in vivo* drug concentrations and QT prolongation to predict QT at some dose
- Approaches to determining ECG assay quality and sensitivity that would be more efficient than the positive control studies recommended in the current guidelines
- Differences in the susceptibility of men and women to drug-induced QT prolongation

Recently, a subset of the data in the ECG Warehouse was placed in the hands of the Cardiac Safety Research Consortium (CSRC), a public–private partnership between FDA and the Duke Clinical Research Institute. These data have been used by software developers to validate algorithms for automated measurement of the QT interval.

Streamlining assessment of the QT interval

TQT studies are costly, and streamlined alternatives could be highly beneficial for new drug development. . FDA is collaborating with the CSRC, and the Consortium for Innovation and Quality in Pharmaceutical Development in a design and conduct a clinical study in healthy subjects to determine if the dedicated TQT study can be replaced by analysis of ECG data generated from First-in-Man single ascending dose studies[2] (these are established components of early clinical development). Six marketed drugs with a well-characterized QT effect are now being evaluated in a "SAD-like" study in healthy volunteers using exposure-response analysis as the primary method.[3]

[2] In this kind of study increasing doses of a new drug are given to small groups of individuals, often up to a maximum tolerated dose.

[3] Darpo B, et al. Ann Noninvasive Electrocar (2014) 19:70-81.

Epidemiologic Studies to Inform the Regulation of Tobacco Products

An FDA/NIH collaboration that collects detailed data on tobacco use and how it affects the health of Americans.

In October 2011, FDA began a collaboration with the National Institute on Drug Abuse (NIDA on the Population Assessment of Tobacco and Health (PATH) Study. The PATH Study is intended to generate detailed data on tobacco use and how it affects the health of Americans. By monitoring and assessing behaviors, attitudes, biomarkers, and health outcomes associated with tobacco product use, the PATH Study is intended to provide a new source of quantitative evidence to help inform regulatory activities and actions under the Tobacco Control Act. The PATH Study is a national, representative, longitudinal cohort study that will follow users and non-users of tobacco products and those at risk for tobacco use ages 12 and older.

Specifically, analysis of the PATH Study data will examine information related to

- What makes people susceptible to tobacco product use
- Initiation and use patterns, including use of new products, multiple products, and tobacco product switching over time
- Patterns of tobacco product cessation and relapse
- Behavioral and health impacts, including emergence of addiction and dependence and tobacco-related disease progression
- Differences in tobacco-related attitudes, behaviors, and health outcomes – across racial, ethnic, gender, and age subgroups and education
- Attitudes, behaviors, and health outcomes in subpopulations, including individuals with mental health or medical co-morbidities, veterans, LGBTQ, pregnant women, and women of reproductive age.

Participants will be interviewed annually for three years; baseline (wave 1) data collection began in September 2013 and was completed in December 2014. Wave 2 data collection began in October 2014. Data collection instruments include a household screener (wave 1 only), an adult questionnaire, a youth questionnaire, and a parent questionnaire. Data are collected in the household via audio computer-assisted self-interviewing (ACASI), computer-assisted personal interviewing (CAPI), and paper questionnaires in English or Spanish. Biospecimens are collected from adults. Ad hoc and topic-based studies (secondary analyses and methodological studies) are also being conducted.

Products assessed in the PATH Study include cigarettes, e-cigarettes, cigars, cigarillos, and little filtered cigars, pipes, hookah, smokeless products, including snus, chewing tobacco, dip, moist snuff, and dissolvable tobacco, and bidis and kreteks (in youth). In addition, product information tracked include brand and variety identification, reasons for use, and perceptions of harm.

PATH Study Accomplishments

To date the PATH Study has:

- Completed the PATH Study field test
- Completed baseline (wave 1) data collection from approximately 46,000 youth and adults and biospecimen collection (urine, buccal cells, and blood) from adults Launched Wave 2 data collection
- Prepared Wave 3 data collection study instruments and materials
- Developed a PATH Study web site with a participant web-page and Spanish translation
- Presented interim preliminary data on approximately half of the cohort at the 2015 meeting of the Society for Research on Nicotine and Tobacco
- Published 20 PATH Study ad hoc studies in scientific journals.

6. Implement a New Prevention-Focused Food Safety System to Protect Public Health

In 2011, the FDA Food Safety Modernization Act (FSMA) was signed into law and gave FDA new and enhanced mandates and authorities to protect public health, redefining the role of FDA's Food and Veterinary Medicine Program (FVM) in safeguarding America's food supply. FSMA directs FDA to build a new food safety system based on the public health principles of comprehensive prevention, an enhanced focus on risk-based resource allocation, and partnership across the public and private sectors to minimize hazards from farm-to-table. To accomplish new mandates under FSMA, FDA continues to build and sustain high-quality, focused intramural and extramural scientific research programs which are providing the foundation for sound regulatory policy, as well as compliance and enforcement actions. Research is needed to fill critical data gaps in our scientific knowledge regarding both the assessment and management of food safety hazards (e.g., microbial and chemical), and to support the development and application of the analytical tools to manage and prevent those food safety risks. This research is critical because it is not conducted by other public or private entities, but is fundamental to the fulfillment of FDA's statutory responsibilities to protect and promote the public health under FSMA.

The following examples illustrate the range of accomplishments in this area of regulatory science:

- Released FDA's 2012–2016 Food and Veterinary Medicine Program Strategic Plan, which identifies key goals and objectives to advance food safety, nutrition, and animal health (This strategic plan includes a new vision and mission statement, a cross-cutting goal, and seven program goals requiring action and dedicated effort over a five-year period.)

- Created a Science and Research Steering Committee (SRSC), which includes science and research leaders from relevant FDA operating units, offices, and centers (The SRSC's primary role is to lead, coordinate and unify research and methods development strategies across the Foods and Veterinary Medicine program.)

- Developed new validation guidelines for chemical methods and analytical methods for detecting microbial pathogens in foods to ensure they meet the highest analytical performance standards for their intended purpose. (These criteria now apply to all FDA laboratories that develop and participate in the validation of analytical food methods for Agency-wide implementation in a regulatory capacity.)

- Expanded FDA's network of veterinary diagnostic laboratories (Vet-LIRN) from the original 16 members in 2010 to 34 laboratories in 2014,. These laboratories have also been heavily involved in CVM's investigation of the illness in dogs associated with eating jerky pet treats (Since 2011, Vet-LIRN has conducted more than 1,000 tests on jerky pet treat samples.)
- Enhanced the National Antimicrobial Resistance Monitoring System (NARMS) to test outbreak strains, link with other federal food safety surveillance programs, expand retail meat testing, enhance collaborative research, and develop new IT tools for data

management and analysis (Surveillance and testing is also being extended to isolates from animal production facilities, to cover the complete spectrum from farm to fork.)

- Developed and evaluated software tools that can perform non-targeted screening using data from a wide range of analytical instruments to determine the presence of unexpected adulterants and contaminants in FDA-regulated products

- Developed FDA-iRISK®, an interactive tool that can compare and rank public-health risks from contaminants (chemical and microbial) in foods (This risk assessment tool generates results relatively quickly and is available to the public at www.foodrisk.org.)

- Developed approaches to use new and emerging technologies for the detection and confirmation of veterinary drug residues in animal-derived food products including animal feeds.

- Created the GenomeTrakr project, a collaboration between FDA, 14 state public health laboratories and nine FDA field laboratories to use WGS for characterization of foodborne bacteria and as a new molecular epidemiological tool to rapidly investigate outbreaks of foodborne illness.

- Established the Coordinated Outbreak Response and Evaluation (CORE) Network to manage not just outbreak response, but also surveillance and post-response activities related to incidents involving multiple illnesses linked to FDA-regulated human and animal food and cosmetic products.

Fighting the Public Health Impact of Antimicrobial-Resistant Foodborne Bacteria

The use, and sometimes inappropriate use, of antimicrobials in both human and veterinary medicine over the past 50 years has given rise to a selection pressure unprecedented in the history of microbial evolution. As a result, we face one of the most critical public health concerns of our time—emergence of bacterial pathogens displaying resistance to many, and in some cases all, clinically effective antimicrobials. Recognizing that antimicrobial use in food animal agriculture and veterinary medicineis a contributing factor, FDA is addressing this public health issue on a number of fronts including:

- Phasing out use of medically important drugs for production purposes in food-producing animals (e.g., for growth promotion), and bringing the remaining therapeutic uses of such drugs under the oversight of licensed veterinarians.
- Enhancing research and surveillance efforts to reduce drug-resistant bacteria in foods and/or feeds and in animals that enter the food supply,
- Strengthening data collection and reporting related to antimicrobial drugs used in food-producing animals and
- Working with Federal and international partners to formulate global strategies to combat antimicrobial resistance (AMR).

Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals

Over the past two years, with broad public input from the public health, agriculture, pharmaceutical, and veterinary communities, FDA has developed and implemented important guidance documents aimed at controlling the development of AMR related to use of antimicrobial drugs in food-producing animals. These guidances outline:

- A strategy to limit medically important antimicrobial drugs to uses that are considered necessary for assuring animal health; and to limit such drugs to uses that include veterinary oversight or consultation,[1] and
- Information on how the animal pharmaceutical industry can voluntarily align their affected products with these recommendations over a 3-year timeline.[2] All of the affected sponsors have agreed to implement the changes outlined in the guidance.

Tracking Antimicrobial Resistance in Foodborne Bacteria

The National Antimicrobial Resistance Monitoring System (NARMS) is a national public health surveillance system that tracks antibiotic resistance in foodborne bacteria.

Critical improvements to NARMS since the Mission at Risk Report include:

- adding capability in 2013 to acquire random, nationally representative samples from food-producing animals at slaughter,
- strengthening formal links with other food surveillance networks (e.g., FoodNet) to

[1] FDA guidance for industry GFI # 209: *The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals*

[2] FDA guidance for Industry *GFI # 213: New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209*

identify foodborne outbreaks involving multidrug-resistant pathogens, including the recent Foster Farms outbreak that sickened over 500 people due to contaminated chicken, and

- formal meetings with CDC, and USDA to discuss the potential impact of new laboratory advances (e.g., whole genome sequencing) on NARMS and determine a collaborative plan of action.

FDA is integrating whole genome sequencing technologies into the NARMS program to provide definitive information on the nature, origin, and spread of resistant bacteria in foods. Recent cooperative research accomplishments include:

- Providing the first completed genome of *Campylobacter coli* with a self-transmissible plasmid conferring resistance to gentamicin, kanamycin, streptomycin, streptothricin, and tetracycline, and
- Identifying the first *E. coli* isolates recovered from U.S. retail meats possessing the *bla*CTX-M beta-lactamase gene and determining that it is carried on a highly transmissible plasmid.

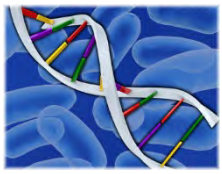
Strengthening Data Collection and Reporting Related to Antimicrobial Drugs Used in Food-Producing Animals

FDA has recently taken important steps to improve data collection and reporting related to antimicrobial drugs used in food-producing animals by:

- Providing more data to the public in the Agency's annual reports summarizing data received from industry on sales of antibiotics approved for use in food-producing animals,
- Soliciting public comment on possible enhancements to the requirements related to collection and reporting of antimicrobial drug sales and distribution data and alternative methods for monitoring antimicrobial use in food-producing animals,
- Initiating a collaborative effort with the USDA and CDC to identify possible approaches for further enhancing current data collection efforts, focused on identifying meaningful metrics for assessing the effectiveness of Guidance 213[2] in actual use (exposure) on the farm and
- Collaborating with Cornell University through the National Institute of Mathematical and Biological Synthesis (NIMBioS) to develop new mathematical modeling methodologies to inform the approach to monitoring and assessing the impacts of the implementation of GFI #213.
- To identify actions needed to address the emerging threat of antibiotic resistance, the Interagency Task Force on Antimicrobial Resistance (consisting of FDA, NIH, and CDC) developed the *Public Health Action Plan to Combat Antimicrobial Resistance*
- Collaborating with WHO to build laboratory capacity for detection of antibiotic-resistant foodborne pathogens and resulting illness, and
- Participating in the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR), created in 2009, with the goal of improving cooperation between the United States and the European Union in (1) appropriate therapeutic use of antimicrobial drugs in medical and veterinary communities, (2) prevention of health care and community-associated drug-resistant infections, and (3) strategies for improving the pipeline of new antimicrobial drugs.

Integrating Genomic Science into the Control of Foodborne Diseases

FDA is collaborating on initiatives to integrate whole genome sequencing into surveillance of foodborne microbial pathogens and establish a central database of foodborne pathogens



Each year, according to the CDC, 48 million Americans acquire a food-related illness and 3,000 die from their infection. In response to this public health challenge, FDA is leading a set collaborative initiatives designed to integrate advances in whole genome sequencing into surveillance of foodborne microbial pathogens. Because even a single change in a sequence of millions of nucleototides may be the only difference between a pathogenic organism and harmless variant, traditional approaches (for example, digesting DNA, separating large fragments, and comparing size distributions) often lack the resolution to allow investigators to identify the source of an outbreak. Recent advances in next-generation sequencing make it feasible to rapidly sequence the entire genome of a suspected pathogen and establish unequivocally whether two isolates are identical or different. A central database encompassing the full diversity of foodborne pathogens will be a critical component of the genomic approach to surveillance and allow researchers to understand how a given pathogen may have originated and even predict the likelihood of the appearance of additional pathogens of a given type or in a given location.

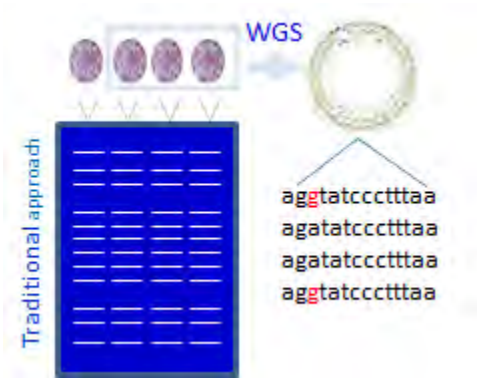
Whole genome sequencing is already transforming surveillance of foodborne pathogens:

- *In 2012, genomic data allowed FDA to trace the source of Salmonella* Bareilly *outbreak in the United States to a fish processing plant in South India.*
- *In 2013, whole-genome sequencing by FDA was used to pinpoint the origin of deadly outbreak of Listeria* monocytogenes *to a cheese manufacturing plant in Delaware.*

Since the Mission at Risk Report, two critical FDA initiatives to realize the promise of whole genome sequencing have been launched:

The Genome Trakr Network

In collaboration with the CDC, USDA, and academic institutions, FDA has created a network of 18 State and Federal laboratories equipped with desktop DNA sequencers and expert staff to collect genomic data from foodborne pathogens. A critical component of Genome



"When we brought whole genome sequencing into the laboratory we had no idea that we would be using it to push back the frontiers of outbreak response … it was like going from using a Gallilean telescope to the Hubble telescope in terms of resolution," Eric Brown, FDA. Because it furnishes complete sequence information, whole genome sequencing (WGS) can unequivocally determine if a pathogen isolated from a patient could be from a given food source.

TrakR will be a public access database supported by NCBI[1] to compare sequences of unknown isolates

[1] In cooperation with the DNA Data Bank of Japan and the European Microbiology Laboratory.

against those previously collected to get forensic leads. Researchers around the world will be able submit genomic data and analyze and compare data in real time, and thus vastly accelerate investigations and contamination control. These archived data will become the foundation for national and international research platforms, such as the Global Microbial Identifier. [2]

- *The number of genomic sequences generated by GenomeTrakr has increased from less than 500 in 2010 to over 2500 today and is now increasing at a rate of 500/ month.*

The 100K Pathogen Genome Project

The 100K Pathogen Genome Project is a consortium consisting of FDA, the University of California at Davis, and Agilent Technologies[3] that is creating a publicly available genetic database of the most common foodborne disease- causing microbes. The goal is to complete and make available 100,000 genomic sequences of foodborne pathogens, an unprecedented extent of genetic data, within the first five years of the project. With allowance for an academic publication window, access to the genetic database will be public. The project is intended to deliver a genetic catalog of some of the most important outbreak organisms that impact human health. Additional scientific deliverables will include:

- new diagnostic testing methods
- insights into molecular basis of infection and drug resistance for use in defining new vaccines and therapies
- genetic biomarkers associated with persistence, antibiotic resistance, pathogenesis, and host association.

Ongoing collaborative research between CVM and CFSAN has also integrated genomics into the National Antimicrobial Resistance Monitoring System (NARMS) by offering scientific, bioinformatics, and technical support on molecular genomic subtyping of their multidrug resistant (MDR) bacterial pathogens. By fully integrating aspects of NARMS to the new genomic technologies, FDA has provided research leadership to investigate the evolution of antimicrobial resistance in zoonotic pathogens and their mobile genetic elements. This information is necessary to inform FDA's policy and regulatory decision making on antimicrobial use in food-producing animals and the process of how foodborne pathogens are entering into the food supply.

[2] The Global Microbial Identifier (GMI) is an international platform for storing whole genome sequencing (WGS) data of microorganisms, for the identification of relevant genes and for the comparison of genomes to detect outbreaks and emerging pathogens.

[3] Also participating are Mars Incorporated, NCBI, and the CDC.

7. Facilitate Development of Medical Countermeasures to Protect Against Threats to U.S. and Global Health and Security

Since 2010, with the launch of MCMi, FDA has greatly expanded its efforts to advance regulatory science related to this category of FDA-regulated products to create the tools that can support regulatory decision making. Priority research areas include: developing animal models and tools to evaluate product safety and efficacy; identifying and qualifying biomarkers for safety and efficacy; using protein engineering to stabilize vaccine proteins; developing methods to assess MCM product quality and related product release assays; validating next-generation *in vitro* diagnostics platforms; assessing the performance of emergency medical equipment; and enhancing emergency preparedness and response capabilities, including risk communication and tracking and evaluating the safety and clinical benefit of MCMs used during public health emergencies.

The following examples illustrate the range of cutting-edge research being supported in this area of regulatory science:

- Developing models of radiation damage in lung, gut, and bone marrow organs-on-chips and then using these models to test candidate MCMs to treat such damage
- Mapping immune responses to certain biothreat agents and MCMs in humans and animal models to create species-specific immune function maps
- Examining the scientific basis for the instability of the protective antigen that has hindered efforts to develop next-generation anthrax vaccines and used protein engineering to stabilize the antigen[1]
- Developing new approaches for measuring the quality of next-generation smallpox vaccines
- Developing new methods for evaluating the purity and sterility of novel cell substrates that can be used to produce vaccines
- Developing new and improved tests to detect viruses and mycoplasma in biological samples including cell substrates and other starting materials to support assessment of product quality, safety, and consistency
- Developing methods for real-time detection of medical device surface contamination to decrease the potential for the transmission of infection between patients as well as between patients and health care workers
- Assessing the feasibility of using electronic health record systems to conduct near real-time monitoring of health outcomes, including serious or unexpected adverse events associated with MCMs used during public health emergencies
- Developing a high-density microarray for detection of over 4,000 antimicrobial resistance genes from bacterial pathogens to accelerate treatment decision making and improve MCMs in the event of a deliberate release of bacterial threat agents or an emerging bacterial disease outbreak

[1] See for example, Verma, A. , et al., (2013) Infect Immun 81:278-84

Validating Next-generation Sequencing Within a Regulatory Framework

FDA and NIST are collaborating to develop reference materials, data, and methods to assess performance of various whole genome sequencing techniques now used or in development.

Since completion of the Human Genome Project in 2003, technical advances have made it feasible to sequence the entirety or large portions of a patient's genome and reveal genetic information that can explain the origins of a disease or help to guide treatment. In what is called next-generation sequencing, (NGS) DNA is cleaved into small pieces that can be individually sequenced, and complex mathematical algorithms are used to identify the part of the genome from which the pieces originated, and thus to re-assemble the fragments into a whole. The sequence obtained can then be compared to a defined "reference sequence" to identify where mutations have occurred in specific genes.

Application of next-generation sequencing (NGS) in the clinical setting is not without challenges. Several different DNA sequencing technologies and computational approaches may be used to obtain an individual's sequence. None are perfect, and for a given sample, they will produce similar, but not identical results. Built-in biases of individual approaches as well as what are essentially "blind spots" mean that in a sequence of over three billion bases, there may be hundreds of thousands of errors in the sequence depending on the approach used and the sample quality. This kind of error rate has important implications for use of NGS in the clinic.

The Genome in a Bottle Consortium

In an effort to assure the introduction of high quality NGS into precision medicine, FDA is collaborating with the National Institute of Standards and Technology (NIST) and providing significant resources to NIST's Genome in a Bottle Consortium to develop the reference materials, reference data, and reference methods needed to assess performance of the various approaches to whole genome sequencing now in use or development. Major achievements of this consortium in the past two years include the following:

- **The Consortium has prepared thousands of DNA samples of a particular genome and is making it available to those developing sequencing technologies and their applications, as well as to laboratories who want to assure their own pipelines are working as expected.**

This reference DNA furnishes investigators with a common standard with which they can compare to understand the accuracy of their sequencing, and to help developers in building new technology approaches.

- **Genome in a Bottle investigators have developed methods to integrate sequencing data sets from multiple sequencing technologies, taking into account the particular biases of each technology, to establish areas of the genome where sequence is known with high confidence**

This has enabled them to produce a highly accurate reference genome corresponding to their DNA sample, which can serve as a benchmark that groups developing sequencing approaches and clinical applications can use to assess, and improve, the accuracy of their methods.

- **The investigators have collaborated with software developers to allow anyone to compare sequences from different bioinformatics approaches to the Consortium's results in an interactive environment.**

By supporting the Genome in a Bottle consortium FDA is establishing the risk-based regulatory framework needed to ensure the validation and quality of specific genetic tests developed by clinical laboratories.

Another accomplishment resulting from FDA's proactive efforts in the NGS domain are the recent FDA clearances for marketing of four NGS-based devices. These devices include the first FDA-cleared NGS instrument, as well as two NGS-based tests that detect DNA changes in the gene responsible for cystic fibrosis: the Illumina MiSeqDx Cystic Fibrosis 139-Variant Assay, which detects known variants in the gene, and The Illumina MiSeqDx Cystic Fibrosis Clinical Sequencing Assay, which sequences a large portion of this gene to detect any differences in the patient's gene compared to the normal gene.

Evaluating the Risk of Guillain-Barré Syndrome (GBS) linked to the 2009 influenza A (H1N1) monovalent vaccines

To determine the level of risk of GBS and other adverse events following vaccination with 2009 influenza A (H1N1) monovalent vaccines, federal agencies launched a collaborative safety surveillance effort that was unprecedented in size, scope, and complexity.

The emergence of a novel influenza A (H1N1) in 2009 prompted the development of monovalent vaccines to protect against this infection. FDA licensed the first influenza A (H1N1) monovalent vaccines on September 15, 2009; in October the vaccines were distributed to the public. This pandemic prompted the largest mass vaccination campaign in recent history.

An unprecedented surveillance effort for GBS

In 2011 the Institute of Medicine published a report* that concluded "the evidence is inadequate to accept or reject a causal relationship between influenza vaccine and GBS." However, a previous national effort for rapid vaccination of the U.S. population against H1N1 influenza (1976 swine flu) was halted due to an association between the vaccine and increased risk of GBS. In anticipation of concerns relating to the latter, the federal government proactively developed numerous complementary strategies to monitor GBS and other possible risks associated with the 2009 H1N1 vaccines. Drawing on the experience and adaptability of its clinical, epidemiological, and statistical experts, federal agencies launched a safety surveillance effort that was unprecedented in its size, scope, and complexity.

In conjunction with CDC, state health departments, academia, industry, health care providers, Department of Defense, Brighton Collaboration, and the World Health Organization, FDA initiated and implemented an extensive analysis of GBS and other adverse events following vaccination. This close collaboration of agencies was key to the campaign's success and demonstrated the federal government's readiness and responsiveness to emergencies.

VAERS

Co-managed by the CDC and FDA, the Vaccine Adverse Event Reporting System (VAERS) detects signals of potential adverse events (AEs) linked to vaccine use, which can be used to generate hypotheses that can be tested more rigorously with other data sources.[1] The researchers reviewed VAERS reports that suggested AEs and sought medical records for all reports coded as serious and for reports suggesting GBS and other events of interest. Advanced data mining algorithms were also deployed to identify unexpected and serious safety concerns. The AE profile in VAERS was consistent with that of seasonal influenza vaccines; GBS and anaphylaxis reports were rare, each <2 per million doses administered. This comprehensive evaluation of VAERS data for 2009 H1N1 vaccines and the deployment of novel data mining methods provided a strong foundation for routine monitoring of all FDA licensed vaccines.

PRISM

Thanks to a partnership of FDA and National Vaccine Program office, the Post-Licensure Rapid Immunization Safety Monitoring (PRISM)[2] system was among the first to link public and private data on a national scale for active vaccine safety surveillance and near real-time identification of new safety concerns. PRISM combined vaccine exposure data from state and local immunization information systems with claims data from five large health plans contributing 38 million members. This enabled the

*Adverse Effects of Vaccines: Evidence and Causality; Committee to Review Adverse Effects of Vaccines; Institute of Medicine, 2011.

[1] Vaccine 28 (2010) 7248-7255

[2] Health Affairs November 2012 31:11

monitoring of 14 key health outcomes among almost 3 million people who had received the H1N1 vaccine.

The PRISM study used 3 complementary analytic methods of chart-confirmed GBS. Investigators found a slightly elevated but not statistically significant incidence rate ratio following receipt of inactivated 2009 H1N1 vaccine and no cases following live attenuated 2009 H1N1 vaccine.[3]

MEDICARE-based surveillance

Managed care network databases can under-represent the elderly and not have sufficient statistical power to evaluate very infrequent events. Therefore, starting in 2006, FDA and the Centers for Medicare and Medicaid used Medicare monthly enrollment and weekly claims data to monitor vaccinations and subsequent hospitalizations with principal diagnoses code for GBS within 42 days of influenza vaccination.[4] The comparator was the rate of GBS after seasonal influenza vaccination in 5 previous years. Based on the analysis of approximately 3.3 million H1N1 influenza vaccinations in this population, there was no evidence of elevated GBS risk. This analysis included the largest number of vaccinations ever monitored by prospective active adverse event surveillance and provided timely rate-based comparisons among millions of vaccines.

A second study of the Medicare population was conducted among chart-confirmed cases using a self-controlled risk interval design to compare GBS risk in a predefined post-vaccination risk period with a control period occurring later in the same patient.[5] The self- control design also controlled for the higher risk of GBS due to age.

The study showed a small but statistically significant elevated risk of GBS with the 2009 H1N1 vaccine, estimating a possible increase of 2.8 cases per million vaccinations. The observed risk was substantially lower than that seen with the 1976 swine flu vaccine. After limiting the analysis to a stricter case definition and excluding cases with preceding illness, the association was not statistically significant. The identification, characterization, and refinement of this risk were the result of collaborative efforts of clinical, epidemiological, and statistical experts.

Pregnant Women

Because pregnancy increases the risk of influenza complications in women, the Advisory Committee on Immunization Practices included pregnant women among the highest priority populations for 2009 H1N1 vaccination. An evaluation of VAERS reports of AEs in pregnant women who received 2009 H1N1 vaccine did not identify any concerning patterns of maternal or fetal outcomes.[6]

Meta-Analysis

Since influenza A (H1N1) vaccines are made using the same processes as seasonal influenza vaccines, a meta-analysis was performed to look for a potential link between GBS and the pandemic vaccine.[7] Data were obtained from six AE monitoring systems: Emerging Infectious Diseases Program (CDC), PRISM, Medicare, Vaccine Safety Datalink, Department of Defense, and Department of Veterans Affairs. The study concluded there were 1.6 excess cases of GBS per million people vaccinated, a modest risk consistent with previous estimates of GBS after seasonal influenza vaccination.

Overall, the data support the conclusion that the benefits of the 2009 H1N1 vaccines outweighed the risks.

Moreover, these studies laid the foundation for an integrated, scalable, and responsive new safety framework that strengthens FDA's routine surveillance and prepares it for future pandemics.

[3] Amer J Epi 2012;175(11):1120-1128
[4] Amer J Pub Hlth 2012;102(10):1921-7
[5] Amer J Epi 2013;178(6):962-73
[6] Amer J Ob Gyn November, 2011
[7] The Lancet 2013;381:1461-68

8. Strengthen Social and Behavioral Science to Help Consumers and Professionals Make Informed Decisions About Regulated Products

FDA social and behavioral scientists have expanded and deepened our use of social science methods of inquiry to understand our target audiences and how to communicate effectively with them. We test how the public responds to various potential communication formats, including nutrition labels, educational videos, and placement of information in print and broadcast advertising, using Internet panels as well as in-person participation. In addition to traditional surveys and focus groups, we also are exploring structured qualitative data gathering methods in open meetings to understand the knowledge, values and concerns of the public. By applying social science methods in the context of internal quality improvement exercises, we leverage our own dedicated workforce to improve our communication products and processes. We are developing new methods to integrate quantitative and qualitative social science results with pharmacoepidemiological data to assess communication effectiveness in the use of regulated products, while also expanding our analytical capacity to learn the extent and effect of FDA communications in social as well as traditional media. The results of our inquiries inform our communications about regulated products with the public including health care professionals, and our communication to regulated industry about labeling and advertising.

The following examples illustrate the range of accomplishments in this area of regulatory science*:*

- Conducted detailed economic analyses of new regulations, for example the Unique Device Identification System, including assessment of the costs, benefits, and cost-effectiveness of the action and alternatives

- Conceptualized a novel integrated, multidisciplinary approach to assessing communication effectiveness followed throughout a unified health care system, from FDA release of safety information, through traditional and social media uptake, to patient awareness assessed qualitatively and quantitatively, and finally to quantitative changes in drug dispensing and rates of health outcomes of interest in comparison to controls and compared to rates observed prior to communication issue

- Conducted a research program on facilitating audience understanding of a legally required list of harmful and potentially harmful constituents of tobacco products, starting with focus groups, then using the findings to develop an experiment comparing lists in different formats for three different types of products (cigarettes, smokeless, or roll-your-own), or no list at all (control)

- Completed a randomized study assessing whether quantitative information could be successfully added to television and print advertisements to maximize audience understanding of benefit information in the piece, including the type of benefit information, different combinations of statistical format, and different graphical representations

- Examined usage and preferences regarding device labeling among both home caregivers (using a web-based survey) and health care providers (focus groups followed by web-based survey)

- Facilitated dozens of analyses of publicly available social media traffic on topics of FDA communications

- Released a second, updated edition of the Bad Bug Book, a compendium of pathogens that are found as contaminants of foods. The revised online edition provides updated scientific and technical information about the major pathogens and toxins that cause foodborne illness.

Revising the List of Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke

FDA is using consumer studies to evaluate list formats and types of information on those lists that best inform consumers about the hazards of tobacco chemicals and support their efforts to quit smoking—or avoid starting.

The Family Smoking Prevention and Tobacco Control Act[1] became law on June 22, 2009. This Act, which amended the Federal Food, Drug, and Cosmetic (FD&C) Act, granted FDA new authority to regulate the manufacture, distribution, and marketing of tobacco products to protect the public health.

Among its many provisions, the FD&C Act requires FDA to establish and periodically revise a list of harmful and potentially harmful constituents (HPHCs) in tobacco products and tobacco smoke, by brand and quantity in each brand and sub-brand. HPHCs are chemicals or chemical compounds in a tobacco product or tobacco smoke that cause or have the potential to cause direct or indirect harm to users or nonusers of tobacco products.[2]

Section 904(d)(1) of the FD&C Act requires FDA to publish a list of HPHCs in a format that is understandable and not misleading to a lay person and to publically display this list. Section 904(d)(2) specifies that FDA must conduct periodic consumer research to ensure that the published HPHC list is not misleading to lay persons.

Studies show that information about chemicals in tobacco, such as quantities of nicotine and tar, as well as descriptors linked to them, can mislead consumers. The FD&C Act, as amended by the Tobacco Control Act, prohibits use of the terms *light, mild, low*, or other similar descriptors unless FDA issues an order permitting a modified risk claim. Congress recognized that many smokers mistakenly believed that cigarettes marketed with these descriptors caused fewer health problems than other cigarettes, and that those mistaken beliefs can reduce the motivation to quit smoking. FDA carefully considered this research when designing the initial research to inform HPHC list development and display. FDA conducted formative research and an experimental study to better understand consumer knowledge and perceptions of tobacco constituents.

Formative Research[3]: In May-June 2011, FDA conducted a qualitative study involving 16 90-minute focus groups with adolescent and adult tobacco users and adolescents at risk for beginning tobacco use. The focus groups—in Washington, DC, Nashville, TN, Miami, FL, and Baton Rouge, LA--included 149 participants. The research identified gaps in consumer knowledge and an interest in seeking out information about harmful chemicals in tobacco products.

Selected results include the findings that:

- Most participants believed that tobacco products contain fewer than 50 chemicals (tobacco and tobacco smoke include more than 7,000 chemicals).

[1] Public Law 111-31 [H.R. 1256]. June 22, 2009. Family Smoking Prevention and Tobacco Control Act. Available at: http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM237080.pdf

[2] Guidance for Industry and FDA Staff. "Harmful and Potentially Harmful Constituents in Tobacco Products as Used in Section 904(e) of the Federal Food, Drug, and Cosmetic Act." January 2011. Available at: http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM241352.pdf

[3] Tessman, GK. Consumer Knowledge and Perceptions about Harmful and Potentially Harmful Constituents in Tobacco and Tobacco Smoke: Findings from FDA Focus Groups (PowerPoint). Presented at the Tobacco Products Scientific Advisory Committee Meeting, August 15, 2013. Available at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/RiskCommunicationAdvisoryCommittee/ucm370179.htm

- Most participants believed that tobacco companies add most of the chemicals to increase addiction potential or to improve taste.

- Many believed that tobacco labeled *organic* has no or few chemicals; few knew that chemicals come from the tobacco itself or are produced during the curing process and though tobacco combustion.

- Most participants were confused by the chemical names, quantities, and units of measure presented in prototype HPHC lists.

- Despite expressing interest in seeing an HPHC list, most participants stated they would likely look at the list only once; few thought seeing the list would prompt them to quit.

Experimental Research[4,5]: Based on this formative research, FDA developed HPHC list prototypes and tested them among 3,527 participants in an online experimental study in April-May 2013. The study was designed to assess the effect of different list formats on the ability of consumers to understand the information presented to them, as well as the effect on consumer perceptions of harm from tobacco products. Test subjects were presented with list prototypes with different explanatory information, iconography, and the number of chemicals included. Participants viewed one of six list prototypes and responded to questions to assess comprehension and perceptions of harm. A control group answered questions without viewing a list prototype.

Study findings were as follows:

- *List exposure:* Exposure to any HPHC list, compared to a "no exposure" control group, was associated with both higher comprehension and higher harm perceptions, but not quit intention.

- *List format:* List format did not affect comprehension, harm perceptions, or quit intention for any tobacco product.

- *Inclusion of supplemental information:* Inclusion of supplemental information was associated with higher comprehension and higher harm perception, but not quit intention.

Research Conclusions: Preliminary findings provided a foundation for FDA to build a research program to support development and evaluation of publicly-displayed HPHC information.

As part of the next phase of research, FDA is continuing to determine how best to define "understandable and not misleading" and to publicly display HPHC information. In November of 2014, FDA announced a funding opportunity through the Tobacco Regulatory Science Program (TRSP) for administrative supplements which will be completed in 2016 to:

- Conduct research to best define what it means to be "understandable and not misleading" to a lay person.

- Design a format for displaying information by brand and by quantity in each brand and sub brand, based on best practices and scientific evidence, to increase the likelihood that when such information is put on public display is understandable and not misleading to lay persons.

[4] Johnson, SE. FDA Experimental Study on the Public Display of Quantities of HPHCs: Study Design (PowerPoint). Presented at the Tobacco Products Scientific Advisory Committee Meeting, August 15, 2013. Available at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/RiskCommunicationAdvisoryCommittee/ucm370179.htm

[5] Portnoy, DB. FDA Experimental Study on the Public Display of Lists of Quantities of HPHCs: Analysis & Results (PowerPoint). Presented at the Tobacco Products Scientific Advisory Committee Meeting, August 15, 2013. Available at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/RiskCommunicationAdvisoryCommittee/ucm370179.htm

After completion of the funded research through the administrative supplements, FDA plans to conduct its own studies to assess the effectiveness of various formats for display and answer key questions including:

- What information do HPHC lists convey to consumers?
- How might consumers use the information contained in the lists?
- How do HPHC lists of cigarettes, smokeless tobacco, and roll-your-own tobacco affect consumer beliefs about, and perceptions of, tobacco products, including those not currently under FDA's jurisdiction?

Improving Labeling to Help Consumers Make Better Food Choices

FDA's consumer scientists evaluate nutrition facts formats in support of new labeling regulations

The Nutrition Labeling and Education Act of 1990 gave FDA the authority to require nutrition labeling on foods to reduce consumers' confusion and help them make better food choices while giving manufacturers an incentive to improve the nutrition profiles of foods.[1] In March of 2014, the Agency published a new set of proposed rules amending its 20-year-old labeling regulations. These proposed regulations were informed in part by the social behavioral science research conducted by social scientists at the FDA.

Focus Group Research to understand How Consumers Process Nutrition Information

In 2003, based on its action plan to address continued high levels of chronic diseases and obesity, FDA had conducted focus group research to examine how consumers commonly use nutrition information on packaged foods and what potential changes to the *Nutrition Facts* label would help them make healthier food choices. The study participants consistently indicated that they disliked doing mathematical calculations, and they often made mistakes when determining the caloric and nutritional content of packaged foods. Participants were particularly critical of foods that were labeled as containing more than one serving per container, but were in their opinion usually consumed all at once: "Who would eat half a muffin?" they asked. Most thought these types of products should be labeled as a single serving, and some agreed that a dual column labeling approach where nutrition information was listed both per serving and per container could be an acceptable alternative.

Building on the feedback from the 2003 focus groups, FDA conducted an experiment in 2011 that assessed how certain *Nutrition Facts* format modifications then under consideration would affect consumer understanding and use of the label information. The researchers specifically focused on products that have two servings listed per container but may be consumed in a single occasion. Study participants were shown nutrition information for the same selection of food products but randomly assigned to see the information in one of ten different Nutrition Facts formats (see figure for selected examples).

The main finding was that for single product evaluations—where the participants looked at a single Nutrition Facts label—the single, large-serving-per-container and the dual-column formats generally improved participants' accuracy in answering questions about the foods' nutritional attributes relative to the current label. This corroborated findings from the earlier focus group research and provided social science support for two key proposals in the proposed regulations published in 2014:

1. **A requirement that products customarily consumed in a single eating occasion be labeled as a single serving, and**
2. **A requirement to use dual column labeling, where nutrition information is listed both per serving and per container, for certain products that may be consumed in one or more sittings or shared.**

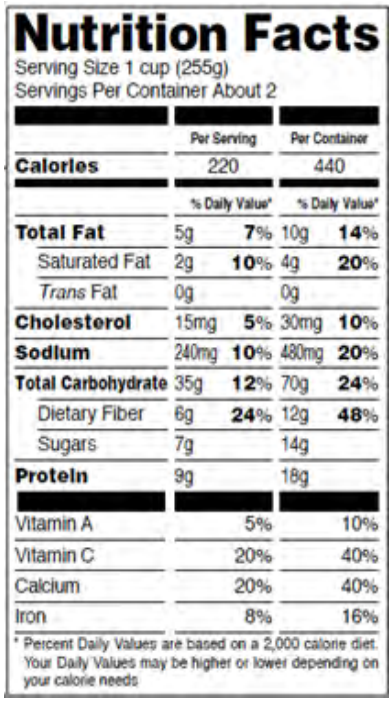
[1] FDA's regulations for the *Nutrition Facts* label went into effect in 1994

FDA began conducting another study in 2014 to examine consumer reactions to declarations of added sugars and to information about percent *Daily Values*. The results should help inform FDA's decision on how best to describe Percent Daily Values on the *Nutrition Facts* label as well as future consumer education initiatives on added sugars.

Emphasize two servings per container

Dual listing for calories only

One serving per container



Gram % DV dual columns
And remove columns from fat

Selected label formats shown to participants in the 2011 study to examine whether certain potential modifications to the Nutrition Facts label would help consumers make more healthful choices. Full Nutrition Facts labels were shown to participants but have been truncated in this Figure. Arrows did not appear on the labels shown to participants, but have been added here to emphasize changes.